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Nalmefene Decreases Meal Size, Food and Water Intake and Weight Gain in Zucker Rats

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McLAUGHLIN, C. L. AND C. A. BAILE. *Nalmefene decreases meal size, food and water intake and weight gain in Zucker rats.* PHARMACOL BIOCHEM BEHAV **19**(2)235–240, 1983.—Opioids are proposed to play a role in the control of food intake since administration of opioids increase food intake while administration of opioid antagonists decrease food intake. In these experiments responses to a new opioid antagonist, nalmefene, were measured in Zucker obese and lean rats. In obese male rats 1 mg/kg nalmefene decreased the size of the first meal after a 10-hr fast and decreased 14-hr food intake, indicating nalmefene is relatively long-acting. Administration of 1 mg/kg nalmefene daily for 7 days decreased average meal size and daily food intake and increased meal frequency; feeding responses on day 7 were similar to those on day 1, suggesting a lack of development of tolerance. Food and water intake and weight gain during a 3-week treatment period were decreased more in lean rats by low doses of nalmefene (up to 0.25 mg/kg) and more in obese rats by higher doses of nalmefene (0.50 mg/kg). These responses to a new opioid antagonist further support a possible role for opioids in the control of food intake.

Opioid antagonists Nalmefene Feeding behavior Food intake Weight gain Obesity
Zucker rats Opiates Meal size Energy balance Endorphins

THE discovery of opioid receptors and endogenous opioids has provided support for the possibility that opioids may be involved in the control of food intake and regulation of energy balance [10, 15, 22]. Administration of the opioids morphine, β-endorphin and enkephalins has increased food intake in rats [7, 20, 25] and fasting has been associated with decreased concentration of β-endorphin in the hypothalamus but not pituitary [5]. On the other hand, opioid antagonist administration decreased food intake [2,4] and, over a period of time, body weight gain [1,23]. In obese animals chronic elevation of β-endorphin reported in pituitary and serum of rats and mice has been proposed to be responsible for increased food intake [18, 23, 24]. Increased response of obese compared with lean rats to the effects of naloxone on food intake further implicates a role for β-endorphin in obesity [13, 17, 18, 23]. However, the evidence for increased β-endorphin as a cause of obesity is yet unclear [6, 8, 24]. In the past, naloxone and longer-lasting naltrexone have been the opioid antagonists used. In these experiments were measured responses to nalmefene (6-desoxy-6-methylenenaltrexone), an opioid antagonist. Nalmefene given orally to rats is 2 times as potent as naltrexone and 48 times as potent as naloxone in antagonizing analgesia induced by 7.5 mg/kg morphine in response to tail clip 30 min later [9]. In addition it is 3.5 times as potent as nalmetrene and 59 times as potent as naloxone in antagonizing analgesia induced by 9 mg/kg morphine in the hot plate test 30 min later [9]. Hahn and Fishman [9] further report that in mice nalmefene is longer-acting and has less opioid agonistic activity than naloxone. Feeding behavior, food intake and body weight gain responses were measured in Zucker obese and lean rats since obese rats have been shown to be more sensitive than lean rats to the effects of naloxone on food intake [18].

METHOD AND RESULTS

In the first of this series of experiments the initial feeding behavior response to nalmefene was measured. Since both initial and subsequent meal sizes were decreased, rats in the second experiment were treated for seven days to determine whether the initial response would be maintained and for how many hours the drug would be effective during the 14-hr feeding period. Experiments 3 and 4 were designed to measure whether decreased food intake would be maintained and would result in decreased body weight gain and whether obese rats would be more responsive than lean rats to chronic administration of nalmefene.

EXPERIMENT 1

Method

Ten male obese Zucker rats (446±46 g) were trained to

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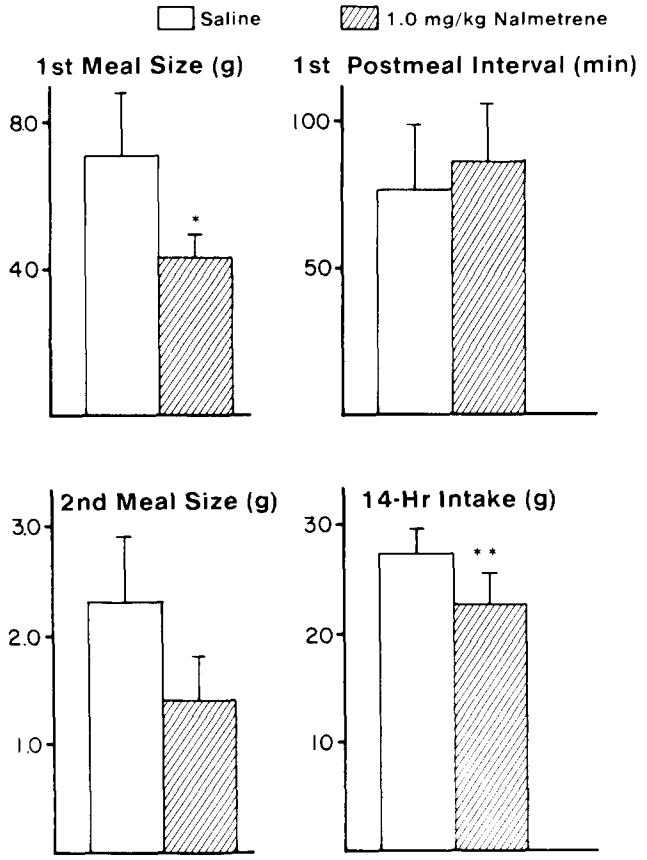

FIG. 1. Feeding behavior response of 8-hr fasted obese male rats (n=10, BW=446±14 g) to SC administration of 1 mg/kg nalmefene or saline. *,**Different from saline, $p<0.05$ and $p<0.01$ respectively, paired t-test.

press a bar to obtain food pellets (45 mg, P.J. Noyes Company) on a continuous reinforcement schedule. They were adapted to having access to food for 14 hr starting at the beginning of the light phase of the 12-hr light-dark schedule. After a preliminary period rats were administered saline (vehicle) or 1 mg/kg nalmetrene subcutaneously just prior to having access to food. A crossover design was used to assign treatments on 2 days 48 hrs apart. Feeding behavior was monitored by recording bar presses on magnetic tape (800 BPI, Kennedy) on a time base with the use of an automated data collection system (Massey-Dickinsen). Data on the magnetic tape were stored and sorted using a Sperry Univac V77 computer. Meals were defined as a minimum of 5 bar presses within 5 min and a minimum 5 min intermeal interval and were summarized for each treatment day. The size of the first and second meals, the interval between the meals and the 14-hr intake were analyzed for significant effects of treatment using paired t-tests.

Results

Administration of nalmefene decreased the size of the first meal ($t=2.58$, $p<0.02$) and 14-hr intake ($t=2.82$, $p<0.01$), but did not significantly affect first postmeal interval or the size of the second meal, Fig. 1.

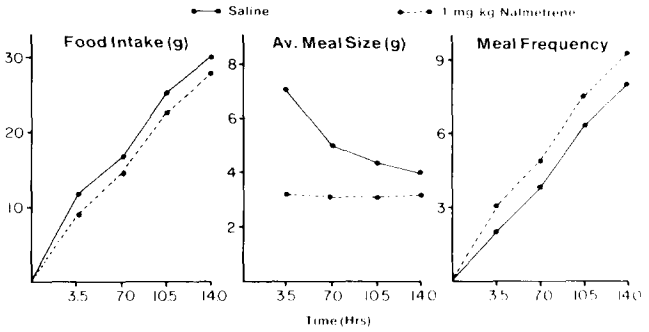

FIG. 2. Average daily food intake (SE=0.7 g), meal size (SE=0.4 g) and meal frequency (SE=0.05) of 10 male obese Zucker rats (327±14 g) administered SC 1 mg/kg nalmefene or saline at time 0 for 7 days. See text for statistical analysis.

EXPERIMENT 2

Method

The ten male obese Zucker rats (327±14 g) which had not been administered an opiate antagonist previously, had been trained to bar press for food and were adapted to the 14-hr feeding schedule were used. During 5 one-week consecutive periods 5 rats (group 1) were administered daily (1) no treatment, (2) 1 ml/kg saline (vehicle) subcutaneously (SC), (3) no treatment, (4) 1 mg/kg nalmefene SC and (5) no treatment. During the same 5 weeks, 5 rats (group 2) were administered daily (1) no treatment, (2) 1 mg/kg nalmefene SC, (3) no treatment, (4) 1 ml/kg saline SC and (5) no treatment. Thus week 1 was a preliminary period, week 5 was a recovery period and week 3 was a recovery period for group 1 and a preliminary period for group 2. Rats were administered treatments just prior to having access to food. Feeding behavior, daily water intakes and body weights were recorded for all 5 weeks and daily feeding patterns were obtained and divided into 4 3.5 hr periods to analyze effects of nalmefene during the course of the day. Since in preliminary analysis feeding patterns on day 1 were not different from those on day 7 of each week, mean values were calculated for each week and these weekly means were subjected to analysis of variance for significance of differences in treatment, time of day, and the interaction of these.

Results

Overall analysis of variance of 14-hr food intake in 3.5 hr intervals showed that there were significant effects of time, $F(3,213)=56.00$, $p<0.001$, with more being consumed in the first period than the subsequent three periods, Fig. 2. Interaction of week with treatment with time was also significant, $F(6,213)=3.20$, $p<0.005$. Post-hoc orthogonal contrasts of the preliminary, treatment and recovery weeks by time indicated that only during the first interval of the treatment weeks was food intake decreased for nalmefene compared with saline treatments, $F(1,213)=5.77$, $p<0.02$. No other comparisons were significant. Thus, the effect of nalmefene was to decrease food intake, but only during the first few hours after treatment. However, it is also clear that the rats did not compensate for the early decrease by consuming more in the other 3 time intervals.

Overall analysis of variance of average meal size revealed

significant effects of treatment, $F(1,215)=3.77$, $p<0.05$, time interval, $F(3,215)=47.50$, $p<0.001$, and interactions of treatment by week, $F(2,215)=5.11$, $p<0.007$, and treatment by time interval by week, $F(6,215)=4.07$, $p<0.001$, Fig. 2. Post-hoc orthogonal contrasts of treatment by time interval revealed that meal size was decreased during the first interval, $F(1,215)=13.56$, $p<0.001$, and across the 4 intervals, $F(1,215)=43.65$, $p<0.001$, but not during intervals 2, 3 or 4. Thus, decreased meal size during the first interval was sufficient, even when meal sizes during the other intervals were not significantly decreased, to result in decreased average meal size across the 4 intervals.

Numbers of meals were affected by time interval, $F(3,210)=15.20$, $p<0.001$, and by interaction of week by treatment, $F(2,210)=3.05$, $p<0.05$, Fig. 2. Orthogonal comparisons revealed that numbers of meals were increased by nalmefene during the first interval, $F(1,210)=11.24$, $p<0.001$, and across the 4 intervals, $F(1,210)=24.93$, $p<0.001$. In addition, across the 4 intervals there were more meals during the week nalmetrene was administered than the week saline was administered, $F(1,210)=8.81$, $p<0.003$. Thus, nalmefene administration decreased meal size and, in spite of increasing meal frequency, decreased total daily intake.

To determine whether tolerance to the effect of nalmefene occurred during the week, food intake, average meal size and number of meals on day 1 were compared with those on day 7 for both saline and nalmefene. Analysis of variance showed that the responses on day 1 were not different from those on day 7 and that compared with saline, nalmefene decreased daily food intake and average meal size and increased meal frequency. These results indicate that tolerance to nalmefene did not develop.

Water intakes were not affected by nalmefene compared with saline treatment (34±2 vs. 36±2 for 14-hr and 37±2 vs. 39±2 for 24-hr periods); however, by orthogonal contrasts water intakes were decreased during nalmefene compared with preliminary period, 34 vs. 38, SE=0.5 ml, $F(1,48)=7.56$, $p<0.005$ for 14-hr and 37 vs. 41, SE=0.5 ml, $F(1,46)=11.08$, $p<0.002$ for 24-hr, but not by saline compared with the preliminary period.

Average daily weight gain, subjected to analysis of variance and orthogonal contrasts showed the weight gain during the treatment (3.6 g) and recovery weeks (3.5 g) were less than during the preliminary week, 4.3 g, SE=0.1 g, $F(1,46)=4.55$, $p<0.02$. Weight gain was decreased by nalmefene, 3.2 vs. 4.5 g, $F(1,46)=9.39$, $p<0.004$, but not by saline (3.9 vs. 4.1 g, NS) when compared with the preliminary period gain, but the weight gain during nalmefene was not different from that during the saline treatment.

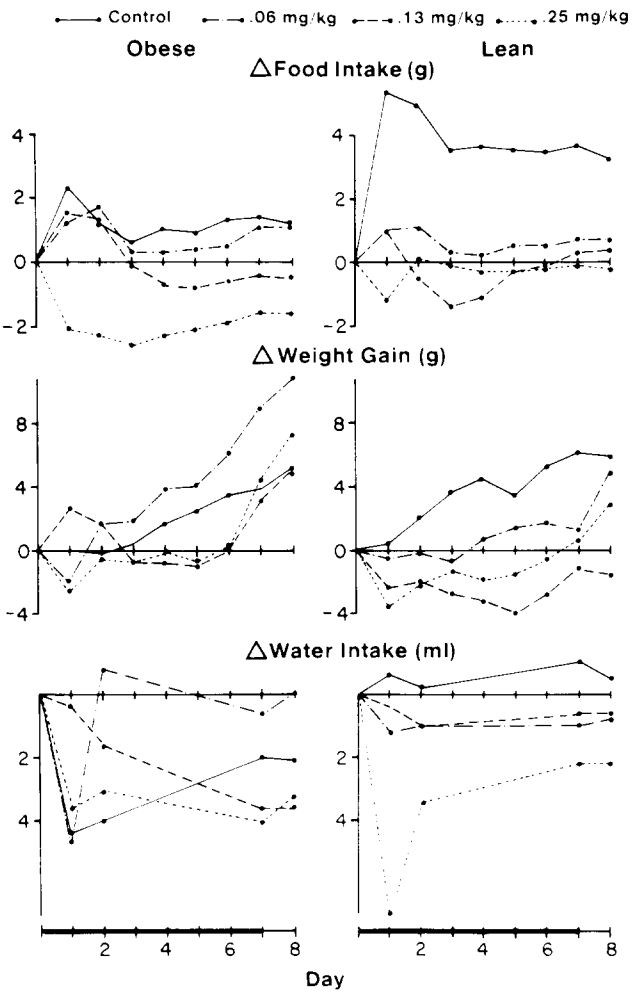

FIG. 3. Change from the preliminary period in food intake (SE=0.09 g), weight gain (SE=0.16 g), water intake (SE=0.34 ml) in male obese (n=20, BW=548±21 g) and lean (n=20, BW=415±11 g) Zucker rats administered SC 0, 0.06, 0.13 or 0.25 mg/kg nalmefene daily for 7 days. See text for statistical analysis.

EXPERIMENT 3

Method

Twenty obese and 20 lean male Zucker rats not previously administered an opioid antagonist were individually housed in a room with constant temperature (21°C) and 12-hr light-dark cycle. The obese rats and their lean pair-mate of the same age were blocked by body weight into 4 groups. After a 7-day preliminary period each group was assigned treatments of SC administration of 0, 0.06, 0.13 or 0.25 mg/kg nalmetrene in saline for 7 days just before the onset of the dark portion of the light-dark cycle. Daily ad lib food intakes (Purina Lab Chow pellets), body weight gains and water intakes were measured during the preliminary and treatment days and on recovery day. Changes from the previous day and cumulative changes during the treatment period were subjected to analysis of variance for significant effects of treatment, phenotype, day and interactions of these.

Results

Food intake. Average food intakes during the preliminary period were 34.0±1.4 and 30.4±8 g for obese and lean rats respectively. Analysis of variance of change from the preliminary period in food intake showed significant effects of day, $F(7,267)=6.88$, $p<0.001$, and interaction of treatment by day, $F(21,267)=4.54$, $p<0.001$, Fig. 3. Post-hoc orthogonal contrasts revealed that food intake was decreased in nalmefene- compared with saline-treated rats only on day 1, $F(1,267)=54.24$, $p<0.001$, and the effect was greater in lean than obese rats, $F(1,267)=8.62$, $p<0.004$.

Weight gain. Average weights at the initiation of the

treatment period were 548±21 and 415±11 g for obese and lean rats respectively. Analysis of variance of weight gains during the treatment period showed significant effects of day, $F(7,252)=5.37$, $p<0.001$, Fig. 3. In lean rats on day 1 weight gain was decreased by nalmefene compared with control treatment, $F(1,263)=3.73$, $p<0.05$. On days 1–7 0.13 mg/kg nalmefene decreased weight gain in lean rats, $F(1,263)=3.70$, $p<0.05$, and 0.06 mg/kg nalmefene increased weight gain in obese rats, $F(1,263)=3.71$, $p<0.05$.

Water intake. Average water intakes during the preliminary period were 40±3 and 37±1 ml/day for obese and lean rats respectively. Changes in water intake were analyzed for day 1, day 2, days 3–7 and 8 (recovery). Analysis showed significant effects of day, $F(3,135)=10.57$, $p<0.001$, and treatment by day, $F(9,138)=2.62$, $p<0.008$. Although water intakes were not decreased across day or phenotype, 0.25 mg/kg nalmefene decreased water intake in lean rats on day 1, $F(1,138)=9.44$, $p<0.001$. On day 8 (recovery) water intakes were increased more in nalmefene-treated than saline-treated rats, $F(1,138)=11.59$, $p<0.001$. This suggests a suppression of water intake was occurring during the treatment period.

EXPERIMENT 4

Methods

Nine male obese and lean, and nine female obese and lean Zucker rats not previously administered an opiate antagonist were housed and fed as in Experiment 3. After a 1-week preliminary period obese-lean pairs of rats of the same age were blocked by weight of the obese rats into 3 groups, each of which was administered 0, 0.25 or 0.50 mg/kg nalmefene in saline SC for 2 weeks just before the onset of the dark portion of the light-dark cycle. One subsequent week was allowed for recovery. Food intakes, body gains and water intakes were measured daily during the 5-week period. Mean values were calculated for weeks 1–4 and changes from the previous week were subjected to analysis of variance for significant effects of treatment, phenotype, sex and week and interactions of these.

Results

Food intake. Average food intake during the preliminary period was 37.6±1.6 and 29.9±1.4 g for obese and lean males respectively and 29.8±1.6 and 21.8±1.2 g for obese and lean females respectively. Analysis of variance of changes in food intake showed significant effects of treatment, $F(2,121)=4.21$, $p<0.02$, and week, $F(3,121)=2.65$, $p<0.05$, and interactions of treatment by week, $F(6,121)=2.93$, $p<0.01$, and treatment by week by phenotype by sex, $F(6,121)=2.32$, $p<0.04$, Fig. 4. Orthogonal comparisons demonstrated that during week 1 food intakes of rats treated with 0.50 mg/kg nalmefene were less than those of control rats, $F(1,121)=10.89$, $p<0.001$, and that treatment of 0.50 mg/kg nalmefene decreased food intake of obese rats more than that of lean rats, $F(1,121)=7.00$, $p<0.009$. Food intakes of rats treated with 0.25 mg/kg nalmefene were increased during week 4, recovery week, $F(1,121)=11.14$, $p<0.001$, and during the 4-week period, $F(1,121)=4.15$, $p<0.04$.

Body weight gain. Average body weights at the initiation of treatments were 539±24 and 392±24 g for obese and lean male rats, respectively and 416±19 and 223±8 g for obese and lean female rats, respectively. Analysis of body weight gain over the 4-week treatment period showed significant effects of phenotype, $F(1,98)=38.94$, $p<0.001$, sex,

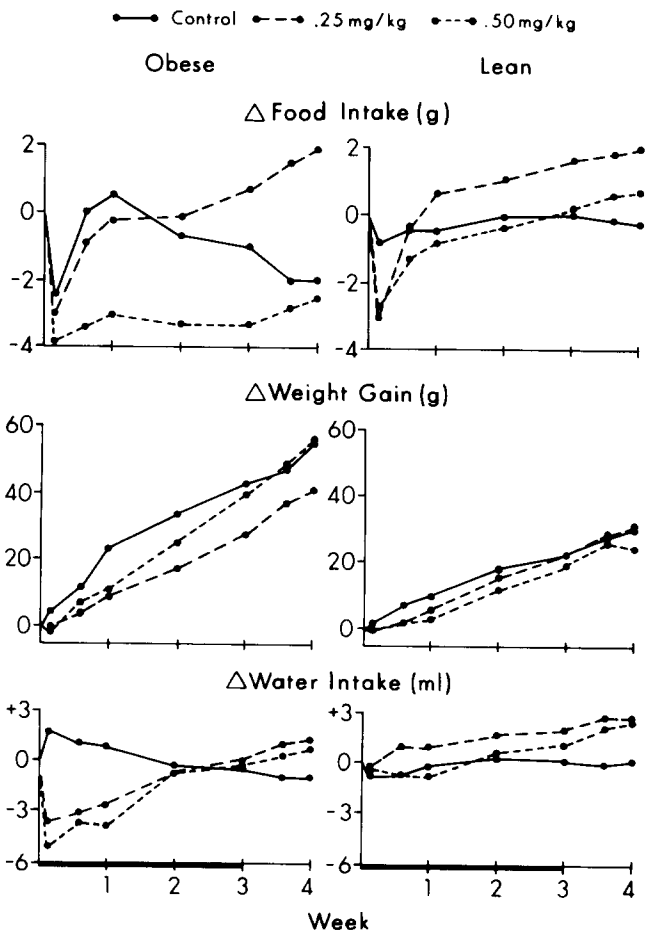

FIG. 4. Change from the preliminary period in food intake (SE=0.13 g), weight gain (SE=0.61 g) and water intake (SE=0.22 ml) in obese male (n=9, BW=539±24 g) and female (n=9, BW=416±19 g) and lean male (n=9, BW=319±24 g) and female (n=9, BW=223±8 g) Zucker rats administered SC 0, 0.25 or 0.50 mg/kg nalmefene daily for 3 weeks. See text for statistical analysis.

$F(1,98)=78.89$, $p<0.001$ and week, $F(3,98)=5.17$, $p<0.002$, and significant interactions of those Fig. 4. Orthogonal comparisons of treatment by week interactions demonstrated that during week 1 weight gain was decreased in nalmefene compared with control-treated rats, $F(1,98)=66.55$, $p<0.001$, and was decreased more in obese than lean rats, $F(1,98)=23.57$, $p<0.001$. However, during weeks 2, 3 and 4 weight gains were greater in rats treated with 0.50 mg/kg nalmefene than control, $F(1.98)=6.29$, 7.07 and 6.55 respectively, $p<0.01$. During the 3-week treatment period 0.25 mg/kg nalmefene decreased weight gain, $F(1,98)=3.85$, $p<0.05$, and the response was greater in obese than lean rats, $F(1,98)=3.84$, $p<0.05$. Also during this period 0.50 mg/kg nalmefene did not affect weight gain across phenotypes because of the interaction of treatment and sex, $F(2,98)=7.27$, $p<0.001$. This dose decreased weight gain in males, 10.2 vs. 13.4 g, $F(1,98)=6.10$, $p<0.02$, but increased weight gain in females, 9.1 vs. 6.5 g, $F(1,98)=3.82$, $p<0.05$.

Water intake. Average water intakes during the preliminary period were 38±2 and 32±1 ml for obese and lean male

rats respectively and were 29±3 and 23±3 ml for obese and lean female rats respectively. Analysis of variance of changes in water intake showed significant effects of week, $F(1,113)=15.95$, $p<0.001$, and interactions of treatment by week, $F(6,113)=5.22$, $p<0.001$, treatment by phenotype by week, $F(6,113)=2.89$, $p<0.01$, and treatment by sex by week, $F(6,113)=2.23$, $p<0.05$. In obese rats water intake was decreased by nalmefene treatment compared with control during week 1, $F(1,113)=5.81$, $p<0.02$, and was increased in nalmefene compared with control-treated rats during weeks 2 and 3, $F(1,113)=12.51$ and 14.83 respectively, $p<0.001$. Nalmefene compared with control treatment during week 1 decreased water intake in male but not female rats, $F(1,113)=5.97$, $p<0.01$, and during weeks 2 and 3 increased water intake across sex, $F(1,113)=16.80$ and 26.46 respectively, $p<0.001$.

GENERAL DISCUSSION

In these experiments nalmefene, a new opioid antagonist, decreased food and water intake and body weight gain in Zucker obese and lean rats. In Experiment 1 the decrease in food intake in response to 1 mg/kg nalmefene was similar to that reported for naloxone [2, 4, 18]. Also, as demonstrated previously for naloxone, nalmefene decreased feeding during the dark portion of the light-dark cycle [3,18]. Under normal feeding behavior conditions the smaller meal consumed after nalmefene treatment would have been followed by a shorter intermeal interval. That it was not, and that there was a trend for the second meal to be decreased, indicated that the influence of nalmefene extended beyond the first meal. In Experiment 2 use of an automated real-time data collection system demonstrated that (1) nalmefene decreased daily food intake because average meal size was decreased even though meal frequency was increased and (2) nalmefene affected feeding behavior primarily during the first 3.5 hr of the 14-hr feeding period. While in studies with naloxone the decrease in food intake was compensated for within several hours [1,3], food intake was decreased for 14 hr after nalmefene treatment, indicating that the rebound which would have been expected of a shorter-acting opioid antagonist was suppressed. Since on day 7 nalmefene decreased food intake as much as on day 1, tolerance had not developed when rats were injected daily just before the 14-hr feeding period.

Chronic administration of relatively long-lasting salts of naloxone and of naltrexone have decreased ad lib food intake and body weight gain as demonstrated in these experiments with nalmefene [1, 17, 23]. However, the doses used in the present experiment (less than or equal to 0.5 mg/kg) are much lower than those used previously (at least 5 mg/kg [1, 17, 23]). Thus, the increased efficacy of nalmefene compared with naltrexone in morphine-induced analgesia tests [9] is paralleled with that in food intake and weight gain tests.

In this as in other experiments in which responses to compounds given to animals of differing weights are compared, the question arises regarding the most valid method of comparing responses. The fact that in these experiments one group of animals had huge adipose tissue depots further complicates the matter. One method of comparison would be to measure the concentration of radiolabelled compound in the serum for several hours after exogenous administration. The doses could be adjusted for the two groups to result in similar concentrations and responses compared. Few studies of this sort have been reported and to accurately reflect the absorption and rate of metabolism of a specific compound that compound would need to be evaluated. These experiments have not been done with nalmefene, thus comparisons must be made on the basis of dose administered. The differences in responses of obese and lean rats in this study are not likely to be due entirely to interaction of administration of doses on a per kg body weight basis and level of adipose tissue because obese rats have responded both more and less than lean rats under specific experimental conditions.

Increased sensitivity to chronically administered naloxone has been demonstrated in obese mice [23] and diet-induced obese rats [17] and has been one of the bases for proposing that increased concentrations of opioids are responsible for increased food intake. However, evidence from several experiments has not supported the hypothesis. For example, β-endorphin concentration in the pituitary is increased in female but not male mice [6], is not increased in all models of obesity [8] and in mice the increase is not evident until 4 months of age, long after the increase in food intake and weight gain has occurred [24]. In addition, not all models of obesity are associated with increased concentration of β-endorphin in the serum or increased sensitivity to the effects of naloxone on food intake [8,26].

In short-term studies the effect of opioid antagonists on water intake has been shown to be independent of its effect on food intake [3, 4, 16] and to be more potent than its effect on food intake [3,16]. When naltrexone was administered to rats for 5 days, water intake was decreased on the first day and remained decreased for the 5 days [14]. In the experiments reported here water intake was consistently decreased during the first week of nalmefene treatment; however, in subsequent weeks water intakes gradually increased. In fact, in some phases of the experiment nalmefene-treated rats drank more than controls. Increased water intake has also been reported in rats administered low doses of naloxone [21]; thus effects of both naloxone and nalmefene on water intake are dose-dependent.

Treatment of females with nalmefene in Experiment 4 revealed an unexpected increase in food intake and body weight gain after the first week. In almost all other studies with opioid antagonists males have been the subjects [1, 3, 4, 5, 11, 12, 16, 17, 25, 26]. When specific comparisons of responses have been made, males differed from females. For example, in obese females but not males β-endorphin concentrations in the pituitary are increased compared with those in lean females and males [6] and females increased water intake in response to low doses of naloxone less than males [30]. Concentrations of circulating prolactin LH, FSH and possibly estrogen are affected by naloxone and hormone responses may differ in females and males sufficiently to affect food and water intake and body weight responses to opiate antagonists.

Nalmefene may exert its effects by a central or peripheral site of action. Jones and Rechter [12] report that naloxone (15 μg) administered bilaterally in the cerebral ventricles decreased food intake while peripheral administration of the same dose had no effect. Unilateral administration of the same dose or of 50 μg did not affect food intake [11,12]. These results, plus the finding that vagotomized rats and rats pretreated with methylatropine do not decrease food intake in response to peripherally administered naloxone, support the likelihood that a central site of action exists [12]. In addition, concentration of β-endorphin in the hypothalamus was decreased with fasting and was increased in the pituitary in some types of obese rodents [6, 20, 24].

While opioids have not definitively been shown to be

components in the hunger-satiety circuit, understanding of the role of opioids and opioid antagonists may lead to their use in attaining desired energy balance.

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