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Opioid Modulation of Ingestive Behavior[1]

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JALOWIEC, J. E., J. PANKSEPP, A. J. ZOLOVICK, N. NAJAM AND B. H. HERMAN. *Opioid modulation of ingestive behavior.* PHARMAC. BIOCHEM. BEHAV. 15(3) 477–484, 1981.—Supportive evidence for an important role of endogenous opioid systems in modulation of ingestive behaviors is presented. Low doses of morphine (1.0–5.0 mg/kg) increase and low doses of naloxone (0.5–2.5 mg/kg) decrease food and water intake during both acute and chronic testing in mildly-deprived rats. Chronic infusions of naloxone with implanted osmotic mini-pumps elicited sustained dose-related suppression of food, water, and saccharin solution intakes but did not reduce ingestion of 10.0% glucose solution or food following 12 hr deprivation. Finally, naloxone treatment did not antagonize nocturnal ingestion of food any more than it reduced day time feeding when the latter was enhanced by prior food deprivation. These results indicate that an opiate agonist and an opiate antagonist modify ingestive behaviors oppositely, affirming that endogenous opioid systems may be involved in control of feeding and drinking. However, their role may be restricted to only indirect participation in homeostatic regulation via neural systems modulating emotional tone or goal-directed behaviors in general.

Morphine Naloxone Feeding Drinking Opioid systems

RELATIVELY pure opiate receptor antagonists such as naloxone and naltrexone suppress ingestive behaviors in rodents [3–6, 11, 13–15]. Naloxone has been reported to be especially effective in reducing overeating in genetically obese mice and rats which have elevated pituitary levels of β-endorphin [21]. Conversely, low doses of morphine injected peripherally [1] and medial hypothalamic or intraventricular injections of β-endorphin [12,17] produce small increases in food intake. Accordingly, endogenous brain opioid systems may be involved in the regulation of feeding and body weight [20].

Nevertheless, evidence for such a role would be strengthened if continuous anorexia were generated by chronic treatment with opiate antagonists. One recent report has provided such evidence by demonstrating long-term suppression of feeding after administration of long-acting suspensions of naloxone [3]. Suppression of feeding was evident for two days but could be sustained for up to five days with daily injections.

The following experiments provide further evidence for the capacity of naloxone and morphine to change food intake in rats: confirming that low doses of morphine and naloxone, respectively, increase and decrease short-term food intake in mildly-deprived rats (Experiment 1); that repeated daily injections of morphine and naloxone continue to produce increased and decreased food intakes (Experiment 2); that chronic peripheral infusion of naloxone induces sustained anorexia (Experiment 3); and that the potency of naloxone in modifying food intake is only slightly different during day and night (Experiment 4). Although opioid participation in the control of food intake is affirmed, alternative hypotheses for these effects are emphasized.

EXPERIMENT 1

In the following experiment, short-term food and water intakes were examined in rats following various doses of morphine and naloxone in a single group of animals.

METHOD

Twenty-four mature Long-Evans hooded rats (9 female and 15 male), 120–140 days old at the start of testing, were housed in standard suspended cages with free access to powdered Wayne Laboratory chow in spillproof glass jars

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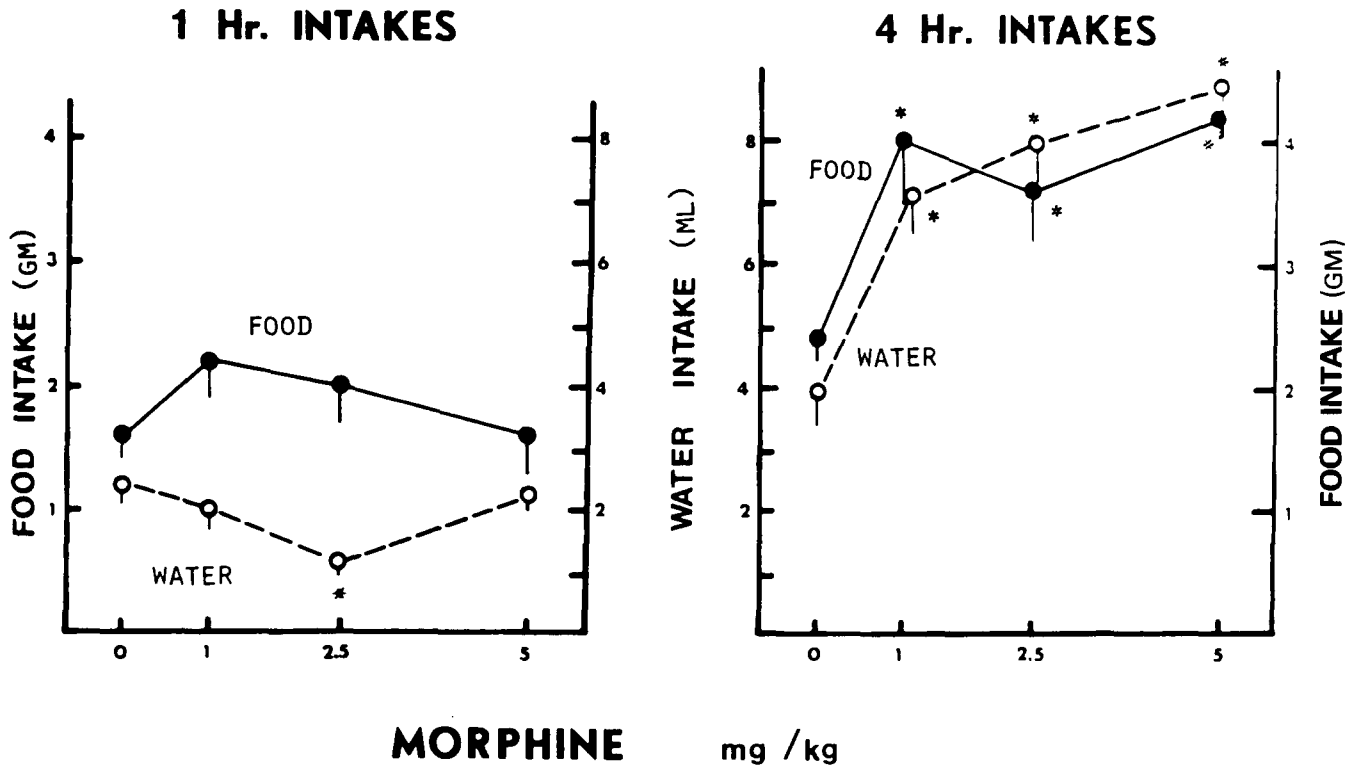

FIG. 1. One and four hour intakes of food and water after subcutaneous injections of morphine sulphate. Means±SEM. *$p<0.05$, control vs experimental, Newman-Keuls test.

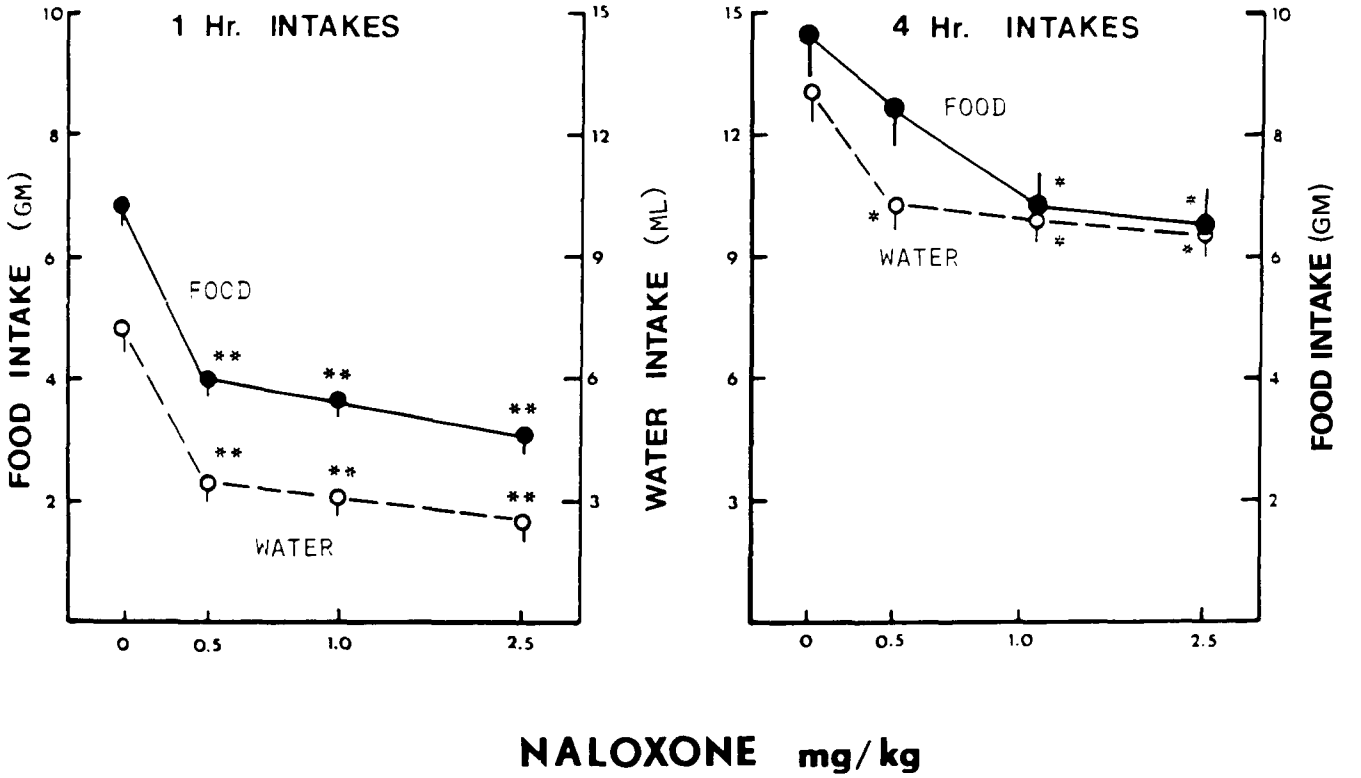

FIG. 2. One and four hour intakes of food and water after subcutaneous injections of naloxone hydrochloride. Means±SEM. *$p<0.05$, **$p<0.01$, control vs experimental, Newman-Keuls test.

and water in calibrated drinking tubes except as noted. Animals were tested in two successive series, the first measuring intakes after morphine administration, and the second, following naloxone treatment.

In the first series, animals were tested following mild (5 hr) food and water deprivation. Their food cups were removed 1.5 hr into the light phase of a 12:12 hr light:dark cycle and they were injected subcutaneously at the nape of the neck 5 hr later with either 0.0, 1.0, 2.5, or 5.0 mg/kg of morphine sulphate in distilled water. Food and water were returned 0.5 hr later and intakes were measured (to 0.1 g and 1.0 ml) at one, four, and 24 hr. All animals were tested under all conditions in a counterbalanced Latin Square design with one full day of ad lib food allowed between successive test days.

Five days after completion of the morphine treatments, the rats were tested similarly following injections of naloxone hydrochloride in distilled water (0.0, 0.5, 1.0 or 2.5 mg/kg). The only procedural difference was the use of a longer preinjection period of food and water deprivation (12 hr) to provide a non-zero baseline for intakes in all animals. Otherwise, measurements were taken at the same times of day as previously.

Treatment comparisons in this and the following experiments were made with ANOVA's as appropriate and the Newman-Keuls test for multiple comparisons.

RESULTS

Intakes of food and water following morphine and naloxone injections are summarized in Figs. 1 and 2, respectively. At one hour, morphine did not affect food intake significantly, but did reliably reduce water intake, $F(3,69) = 3.58$, $p<0.05$. By 4 hr after injection, morphine had increased food intakes reliably at all doses by 50–75%, $F(3,69)=5.47$, $p<0.01$, and water intakes by 90–130%, $F(3,69)=19.00$, $p<0.001$. Mean 24 hr intakes of food (g±SEM) were not significantly different among the various dose levels of morphine: 24.8±5.3, 23.7±5.3, 23.0±5.7, and 22.1±4.3 for the low to high doses. Similarly, mean 24 hr water intakes (ml±SEM) were unaffected: 38±8, 40±8, 39±8, and 38±7 for the low to high doses.

One hour after food and water were returned in the naloxone series, intakes were reduced by 40–54%, $F(3,69) = 42.21$, $p<0.001$, and 53–66%, $F(3,69)=24.79$, $p<0.001$, respectively. Even 4 hr after naloxone injections, food intakes were 13–30% below control levels, $F(3,69) = 9.29$, $p<0.01$, and water intakes were similarly reduced 20–24%, $F(3,69)=24.79$, $p<0.001$. However, as with the effects of morphine on ingestion, 24 hr intakes of food and water were not significantly changed after naloxone treatment. Mean food intakes for the low to high dose groups were (g±SEM): 33.2±7.1, 32.5±6.3, 31.2±5.9, and 30.9±6.1 and water intakes were (ml±SEM): 55±10, 51±10, 54±11, and 53±11.

Individual comparisons between treatment and control scores are summarized in Figs. 1 and 2 and indicate that the above effects were seen at most doses. The exception being one hour water intake following morphine, where only the 2.5 mg/kg dose proved reliable. Generally, the dose-response curves were flat, and yielded few reliable differences: the low dose of morphine yielded less water intake than the high dose at 4 hr ($p<0.05$), the low dose of naloxone was followed by more water intake at one hour than the high dose ($p<0.05$), and the low dose of naloxone reduced food intake

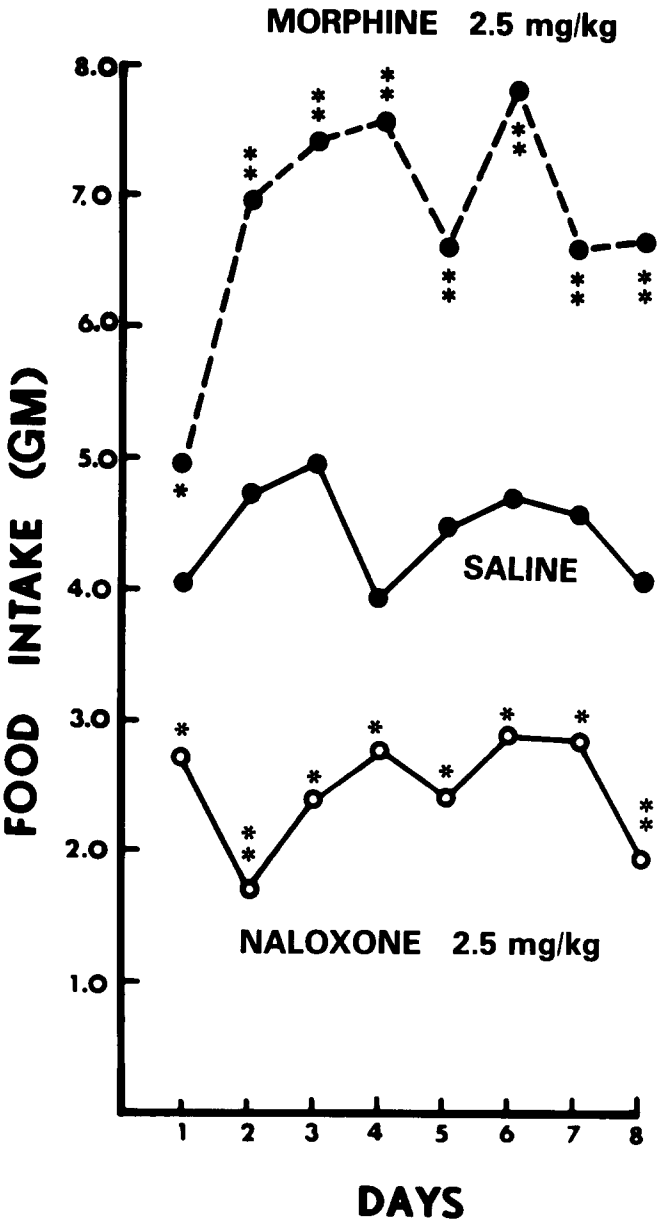

FIG. 3. Mean four hour intakes of food after subcutaneous injections of morphine or naloxone (Experiment 2). *$p<0.05$, **$p<0.01$, saline vs drug, Newman-Keuls test.

less than the medium and high doses at 4 hr (p's<0.05). No reliable differences were apparent between sexes when amounts ingested were compared as intakes/kg of body weight.

DISCUSSION

These results confirm that activation of opioid systems can produce modest increases in food and water intake while blockade of opioid systems can reduce food and water intake in mildly deprived animals. However, clear dose-response relationships were not evident over the range of doses we employed. In both cases, the short-term changes in feeding

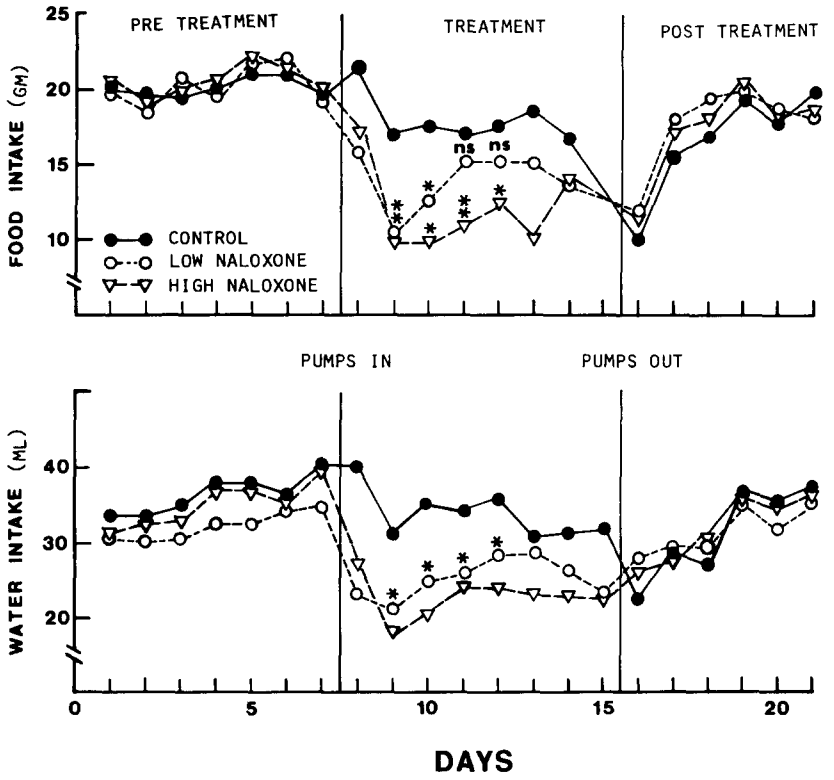

FIG. 4. Mean daily intakes of food and water during chronic infusion of naloxone via subcutaneous osmotic mini-pumps. Low dose=0.32 mg/kg/hr; high dose=0.95 mg/kg/hr. Paired comparisons conducted only for days 9–12: $*p<0.05$, $**p<0.01$, ns=nonsignificant, Newman-Keuls test. For water intake, high naloxone results were not reliably different from low naloxone, but were different from controls.

were compensated for, and no reliable change in 24 hr intake was apparent following either drug.

EXPERIMENT 2

The aim of the following experiment was to determine whether the facilitation and inhibition of food intake by morphine and naloxone, respectively, would be sustained across repeated test days.

METHOD

The animals used in Experiment 1 were divided into three groups (n=8 per group) balanced across sexes. Five days following the termination of Experiment 1, the rats were placed on a schedule where a 5 hr food deprivation period was instituted each morning. At the midpoint of the light cycle, one group of animals was injected with 2.5 mg/kg of morphine subcutaneously, another with 2.5 mg/kg of naloxone, and the control group with an equal volume of the saline carrier. Half an hour later food cups and water tubes were returned and intakes were measured for 4 hr. Eight successive daily tests were conducted, with animals in each group receiving the same treatment throughout.

RESULTS

Average food intakes for the 4 hr following treatment are summarized in Fig. 3. Over the eight test days, naloxone decreased average food intake by approximately 44% and morphine increased intake by about 57% yielding a reliable effect of treatments, $F(2,21)=10.56, p<0.001$, but there were no reliable effects of days or treatment×days interaction. Effects of each drug were sustained for the duration of treatment.

DISCUSSION

These results affirm that the appetite-reducing effect of naloxone and the incrementing effect of morphine remain fairly stable from day to day. The lack of tolerance to the appetite-stimulating effect of morphine contrasts that observed with analgesic responses, and is similar to the lack of tolerance that has been observed with lowering of self-stimulation thresholds [9] and the induction of discriminable internal states following administration of opiate agonists [8].

EXPERIMENT 3

The results of the first two experiments confirm a role for endogenous opioid systems in the control of ingestive behaviors. The second experiment demonstrated that opiate agonist and antagonist effects on food intake can be sustained during a week of daily drug treatments. Nevertheless, the idea that these systems participate in the regulatory control of feeding would gain considerable support if continuous administration of naloxone chronically suppressed food intake. Note that a trend toward a prolonged effect was not present in Experiment 1 where acute injections of naloxone

suppressed feeding during the first hour following administration, but little additional suppression accrued during subsequent hours. However, the results of Experiment 2 and an earlier report [3] suggest possible long-term effects on ingestion. Accordingly, in this experiment we monitored daily food and water intakes in rats during a continuous week-long subcutaneous infusion of naloxone.

METHOD

Eighteen male Long Evans hooded rats (380–400 g) were housed and fed as in Experiment 1. Prior to this experiment, all animals had been habituated to consuming a 0.15% saccharin solution. After one week of monitoring ad lib daily intakes and body weights, all animals were implanted subcutaneously at the nape of the neck with Alzet 2001 osmotic mini-pumps [26] filled with either distilled water, 0.1 mg/μl, or 0.3 mg/μl of naloxone hydrochloride (n=6 per group). Implantations and later removals were done using ether anesthesia. At the nominal infusion rate of 1.0 μl/hr for these pumps, the rats received approximately 0.32 mg/kg or 0.95 mg/kg each hour during an eight day infusion period. Food and fluid intakes were monitored at 12 hr intervals synchronized to lighting transitions during the infusion period and daily for six days thereafter.

Additional tests were conducted during the course of infusions. On day 5 of infusion, all animals were permitted 4 hr of access to 0.15% saccharin and intakes were measured at 10 min, 30 min, 2 hr and 4 hr. On days 6 and 7, animals were deprived of food for 7 hr during the daytime, and the effects of subcutaneous morphine (1.0 mg/kg) or the distilled water carrier on 1 hr food intakes were determined using counterbalanced procedures. To determine whether the suppression of food intake produced by naloxone generalized to a palatable nutritive solution, all rats were permitted 12 hr of ad lib access to a 10.0% (w/v) d-glucose solution in addition to their usual food and water at the beginning of the dark cycle on the seventh day of infusion. In order to evaluate the capacity of these animals to respond to acute starvation, all were food-deprived overnight for 12 hr on day 7 and the amount consumed during a 1 hr feeding period was determined. Finally, on the last day of infusion, just prior to excision of the pumps, we verified the potency of opioid blockade by determining if circulating levels of naloxone were sufficient to antagonize morphine analgesia. All rats were injected with morphine (15.0 mg/kg, IP) and an alligator clip was applied to each animal's left hindlimb. The latencies to an audible squeal were recorded (±0.1 sec) with a maximum permissible score of 15 sec.

RESULTS

Mean daily food and water intakes for the three experimental groups are summarized in Fig. 4. The overall statistical analysis was limited to data from days 2–5 of infusion because the maximal effect required a day to appear (perhaps partially because of a warm-up period needed for the pumps to become operational), and because of the many additional manipulations executed during the last 3 days of the infusion period. During this period both groups receiving chronic naloxone infusions exhibited reduced food, $F(2,15)=13.18$, $p<0.001$, and water intakes, $F(2,15)=16.68$, $p<0.001$, and the effects were more pronounced in the high-dose group. The only other reliable effect was days for feeding data, $F(3,45)=5.01$, $p<0.01$, suggesting the presence of some tolerance to the anorexigenic effect of naloxone, especially in low-dose animals. The nocturnality of feeding was not affected substantially by the naloxone treatments, since low and high-dose naloxone animals on the average consumed 83% and 78% of their food at night while controls ate 86% of theirs in the dark. In absolute terms, however, most of the depression in food intake occurred at night, with a mean reduction in the low-dose animals of 3.6 g/day and in the high-dose group of 5.9 g/day. The mean daytime reduction was 0.2 g/day for both groups. Following termination of the infusions, food intake gradually returned to normal with no compensatory hyperphagia. During the infusion period, rats in the vehicle-treated group lost an average of 7 g of body weight while those in the low and high-dose groups lost 11 and 18 g, respectively, $F(2,15)=7.91$, $p<0.01$. Only the latter effect was reliably greater than control losses ($p<0.01$).

During access to saccharin, control animals drank 6, 10, 12, and 20 ml at the successive measurement periods, while the low-dose rats drank 6, 7, 8, 10 ml, and the high-dose group 5, 6, 8, 10 ml (mean intakes). The effects of treatments, $F(2,15)=7.19$, $p<0.01$, time, $F(3,45)=47.55$, $p<0.001$, as well as their interaction, $F(6,45)=6.03$, $p<0.01$, were reliable, indicating that the suppression of intakes in the naloxone-treated animals was due primarily to a lack of sustained intake as opposed to a suppression of the initial acceptance of saccharin solution.

After acute injection of morphine, the average food intake in the control group increased from 0.7 to 1.7 g, ($t=2.93$, $p<0.05$; one hr intakes), while intakes in both the low and high-dose groups remained essentially unchanged (0.6 to 0.8 g). Mean twelve hour intakes of 10% glucose (ml±SEM) were not reliably different between the carrier, low, and high-dose groups (62±6, 76±11, and 63±5, respectively). One hour intakes of food (g±SEM) were similar for the three groups—3.7±0.8, 4.4±1.1, and 4.1±0.5, respectively. The results of the morphine-analgesia test indicated that both levels of naloxone infusion produced resistance to morphine analgesia. Typically, normal rats squealed promptly (0.1–0.2 sec) to our nociceptive stimulus. After morphine, it took 10.2 sec for controls to respond, while for low and high-dose groups the mean latencies were 1.1 sec and 1.5 sec, respectively (p's<0.001).

DISCUSSION

The results of this experiment demonstrate that chronic opioid blockade can produce long-term suppression of food and water intake and suggest strongly that endogenous opioid systems may participate in the regulation of feeding. The fact that initial preference for a non-nutritive sweet solution (saccharin) was not modified by opioid blockade whereas sustained intake was inhibited suggests that opioid systems may be related to some positive sensory feedback system that normally sustains food intake, for instance, the central mediation of the incentive properties of food [19]. Still, the fact that a similar suppression of intake was not observed with the 10.0% glucose solution, might suggest that the aversive gustatory quality of saccharin was critical in lowering intake. Perhaps opioid receptor blockade amplified this characteristic.

That our naloxone infusions were producing effective opioid blockade throughout the infusion period was indicated not only by the failure to observe morphine-induced feeding or analgesia in naloxone-infused animals but also by the sustained suppression of feeding and drinking. The abo-

TABLE 1
AVERAGE (± SEM) FOOD INTAKES FOR RATS AFTER SUBCUTANEOUS INJECTION OF NALOXONE (1.0 mg/kg)

		0.5 hr	2.0 hr	4.0 hr
Nondeprived	Control	0.1 (0.0)	0.6 (0.6)	1.6 (1.1)
Daytime	Naloxone	0.1 (0.1)	0.4 (0.4)	0.9 (0.8)†
12 hr Deprived	Control	4.2 (1.0)	6.1 (1.3)	7.3 (1.8)
Daytime	Naloxone	2.5 (1.1)†	3.7 (1.3)‡	5.3 (1.2)‡
Nondeprived	Control	2.4 (1.2)	4.9 (1.9)	7.9 (2.3)
Nightime	Naloxone	1.9 (1.1)*	3.8 (1.8)†	6.8 (1.9)†

*$p<0.05$; †$p<0.01$; ‡$p<0.001$.

lition of morphine-induced feeding strongly suggests that the suppression of ingestion by naloxone was mediated through opiate receptors as opposed to some other mode of action.

EXPERIMENT 4

The previous experiment indicated that chronic naloxone infusions, although inducing stable anorexia, had little consistent effect on the nocturnality of feeding, even though night-time intakes were suppressed more than daytime. This trend is consonant with the ability of naloxone to have a greater hyperalgesic effect at night than during the day [10], but because of marked differences between day and night consumption, the effect could be due simply to differential base-lines. Accordingly, in the following experiment, the effect of naloxone on day and night food intakes was measured following acute naloxone injections when daytime consumption was matched to night-time intake by prior deprivation.

METHOD

Eighteen mature male Long Evans hooded rats were maintained as before with ad lib food and water except as indicated. The animals were given three successive series of tests, where food intake was measured following subcutaneous injections of naloxone (1.0 mg/kg at 0.5 hr before feeding). In the initial series, animals were tested during the first half of the light cycle with no prior food deprivation. In the second series, the same animals were tested during the first half of the dark phase, and to insure immediate food consumption, 2 hr of food deprivation were imposed prior to the feeding test. In the third experiment, food intakes were again monitored after injection of naloxone during the first half of the light cycle, but to insure a level of food intake comparable to that observed at night, food cups were removed 12 hr before the beginning of the test. In each series, animals were given both control and naloxone treatments in a counterbalanced manner with at least one full day of ad lib access to food between successive tests. Food intakes were measured 0.5, 2, and 4 hr following the return of food.

RESULTS

Mean food intakes are summarized in Table 1. Drug effects were reliable in all three series, with the greatest suppression of feeding noted for animals tested in the daytime following 12 hr food deprivation, $F(1,17)=44.68$, $p<0.001$, while for non-food deprived rats injected with naloxone during the light period, $F(1,17)=4.62$, $p<0.05$, and for animals tested during the dark period, $F(1,17)=8.94$, $p<0.01$. With regard to the nondeprived rats tested during the light period, food intakes were reduced 44% ($p<0.01$) but only by the fourth hr after injection, while for dark-tested animals intakes were suppressed 21%, 22%, and 14%, at each of the measurement periods (all p's<0.05) and for food deprived animals tested during the light period, 41%, 39%, and 27%, respectively (all p's<0.01). The control intakes of the latter two groups were similar at the fourth hr after injection yet suppression of food intakes at that time was substantially greater for deprived rats tested during the light period (27% vs 14%: $p<0.05$). Somewhat greater relative as well as absolute differences in intake suppression were evident at the earlier measurement periods but under no condition did naloxone-induced anorexia persist to 24 hr.

DISCUSSION

These results provide no evidence for enhanced antagonism of feeding by naloxone during nocturnal hyperphagia in the rat. Although such a conclusion might have been supported had only non-deprivation conditions been used, when baseline intakes for the light and dark periods were matched by prior food deprivation, suppression of feeding by naloxone was somewhat greater during the relative aphagia of the light period. This suggests that endorphinergic control of feeding may be more influential in promoting feeding during the day than at night. Alternatively, if naloxone-induced anorexia is mediated via a non-homeostatic mechanism such as increased emotionality, the rat may be more receptive to the induction of this state during the daylight hours. These findings do not corroborate the results obtained with painful stimuli to which naloxone elicits greater hyperalgesia in mice during the dark period [10] but do support the cycle-independent effects of naloxone noted earlier [5]. In addition, our results highlight the need to establish comparable baselines for behavior during light and dark periods of the circadian cycle before contrasting differential diurnal effects of drugs.

GENERAL DISCUSSION

The results of these experiments clearly indicate that morphine and naloxone modulate ingestive behaviors in opposite directions, confirming that endogenous opiate systems might participate in normal control of food and water

intake. The most compelling evidence was derived from the finding that chronic infusion of naloxone elicits a relatively stable and sustained reduction in food intake. However, neither our studies nor the work of others provides cogent evidence that opioid systems affect ingestion by acting directly upon energy regulation.

The anorexia induced by naloxone might have been due to illness since this opiate antagonist has been used to condition rejection of sapid solutions [7, 11, 18, 25, 27]. However our findings that the initial acceptance of saccharin, the 12 hr acceptance of glucose, and feeding in response to overnight starvation were normal during the course of chronic naloxone infusion suggest that our animals were not suffering malaise.

Nevertheless, it remains possible that the reduction of feeding and drinking accompanying chronic infusion of naloxone or following acute injections reflects a change in the emotional tone of animals as opposed to a shift in the bias of control systems for energy homeostasis. For instance, social deprivation in young animals leads to striking reductions in body weight [24]. In addition, naloxone treatment can amplify emotional behaviors normally induced by social isolation, such as distress vocalization [24]. Accordingly, it may be that both acute and chronic anorexia induced by naloxone reflect the operation of a non-homeostatic emotional bias on brain feeding control circuits mediated by endorphin systems. Conversely, the increased feeding noted after low doses of morphine might indicate activation of a positive emotional bias. Increased opioid activity could induce a state of comfort during which an animal may exhibit increased appetitive behavior in the same manner that social facilitation can increase feeding [28].

Alternatively, opiates and their antagonists may affect ingestion by modulating central reward processes which may be quite directly involved in appetitive behaviors. In this regard, Belluzi and Stein [2] have implicated endogenous opioid systems in drive-reduction reward. Unfortunately, the most straightforward prediction of their hypothesis, that opiate agonists would decrease feeding, does not hold true. At low doses, which presumably best simulate physiological conditions, morphine increases feeding. A slightly different hypothesis proposed by Frenk and Rogers [11], suggests that the naloxone-induced suppression of feeding is due to reduced ligand/receptor binding and consequent reduction of opiate-mediated reward during ingestion. They also predicted that morphine should suppress ingestion by inducing reward so emphatically as to obviate the drinking of a thirsty animal. Our results demonstrating enhanced ingestion of food and related water intake after morphine do not support either hypothesis.

Clearly, opioid systems are ubiquitous in the brain, and perhaps systemic drug administration strategies will prove inherently confusing because of the multiplicity of systems affected concurrently. For example, morphine can increase behaviors as diverse as play [16,22] and extinction in a T-maze [23], which are outwardly quite remote from ingestion. Of course such diverse phenomena could be coordinated if it is assumed that they share a common nonspecific substrate, such as one which generally activates goal-directed behavior. However, adequate evidence for such a general neural system is not yet available and the winnowing of options will require further study.

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