Naloxone Reduces Food Intake in Humans

MARTIN R. COHEN, MD, ROBERT M. COHEN, MD, PhD, DAVID PICKAR MD, AND DENNIS L. MURPHY, MD

Hypotheses generated from animal studies that the endogenous opioid system is an important modulator of food intake suggest that blockade of the system in humans should affect eating behavior. To assess this hypothesis, seven normal volunteers were given 2 mg/kg naloxone or placebo on separate days in a double-blind, random but balanced cross-over experimental design. Compared to placebo, naloxone was found to reduce significantly total food intake from preselected prepared trays served 2.75 and 7.75 hours after drug administration (p < 0.02). The reduction was considerable (28%), and although the magnitude varied greatly among individuals, reduction occurred in each. This reduced food intake was not accompanied by a demonstrable alteration of the volunteers' perceptions of their hunger. Further cautious experimental investigation of naloxone's effects during long-term administration and in patients with eating disorders is warranted in light of its apparent effect of reducing food intake in humans while not decreasing their satiety.

There is substantial evidence from animal studies that the endogenous opioid system (EOS) is an important modulator of eating behavior (1, 2). An important component of this evidence is the dose-related suppression of food intake produced by the administration of naloxone in the mg/kg range to rodents (3, 4). Because naloxone is considered a pure opiate receptor antagonist, this effect is considered to reflect functional blockade of the EOS and thus active involvement of the EOS in the eating behavior of these animals.

The evaluation of behavioral effects produced by the administration of naloxone has also been a major experimental approach in clinical research. However, clinical research began with the use of doses as low as 5 μg/kg (0.4 mg) and still has not generally exceeded 0.3 mg/kg (20 mg) (5-7). These doses originated from the exceedingly small dose (less than 5 μg/kg) needed to precipitate withdrawal from narcotic alkaloids (exogenous opioids) in humans (8).

We have recently demonstrated dose-dependent behavioral effects of naloxone given to normal volunteers in the mg/kg range that were not evident in previous clinical studies using lower doses (9, 10). Concomitant physiologic and hormonal evaluations supported the continuing specificity of naloxone as an opiate receptor antagonist at these doses. These data suggested that some EOS were not completely blocked at lower doses of naloxone, supporting the presence in humans...
NALOXONE REDUCES FOOD INTAKE

of multiple opiate receptor subtypes and systems differentially sensitive to the blocking action of naloxone (8, 11, 12).

In this study, we evaluated the eating behavior of normal volunteers after the intravenous administration of 2 mg/kg naloxone. This dose was chosen because it was consistent with doses necessary in animal studies to produce suppression of food intake; it was found in our previous study to be safely administered to normals (1, 3, 4) while producing only minimal physical or psychologic effects that might nonspecifically affect eating (9, 10).

METHODS

Seven healthy volunteers (aged 19 to 51 years; mean ± SD, 30 ± 13 years; 5 women, 2 men) agreed to participate in the study after a discussion of the purpose, nature, and possible hazards of the experimental procedure. A physical and psychiatric evaluation eliminated those who were more than 20% overweight, were suffering from a physical illness, or had a history of psychiatric illness or drug abuse. All subjects were required to be free from opiate exposure for at least the 3 weeks before the study and from any medication for at least the 3 preceding days.

Volunteers reported for 2 days of study at least 3 days apart. Each study day began at 0830 hours after an overnight fast. An intravenous catheter was placed in an arm vein and kept patent with heparin. At 0920 hours, 0.4 mg of naloxone was administered intravenously. This small dose was used to eliminate the possibility of undetected or unwitting recent opiate use by a volunteer that could lead to a severe withdrawal reaction after the administration of a high dose of naloxone; opiate use would also complicate any conclusions regarding the effect of high-dose naloxone on the EOS. After this low dose of naloxone failed to produce effects of opiate withdrawal (as was always the case) an intravenous infusion of 2 mg/kg naloxone (dissolved in less than 20 ml normal saline vehicle), or a normal saline vehicle of equal volume (placebo), was administered over less than 2 minutes at 0930 hours. The study used a double-blind, random but balanced cross-over design; each volunteer was given the naloxone and the placebo on separate days.

All studies were conducted in the Clinical Center of the National Institutes of Health on the same inpatient unit. Volunteers were permitted to eat only during designated lunch and dinner periods from prepared trays at 1215 and 1715 hours. Activities that were not physically strenuous were permitted ad libitum within the confines of the unit. However, volunteers were required to lie supine for a period before and after infusions (from 0915 until 1000 hours).

Meals consisted of items preselected by volunteers in portions large enough to ensure that no subject would want to eat more food than was available. The food portions were premeasured and measured again after completion of the meal. Food intake was considered the difference between these measurements. Analysis for calories as well as grams of protein, fat, and carbohydrate was conducted using the nutrient data bank at the Department of Biometry, School of Medicine, Case Western Reserve University, Cleveland.

Using two 100-mm visual analogue scales, volunteers rated their hunger and thinking about food before the day’s infusions as well as at 0.75, 1.5 (before lunch), 4 (after lunch), and 7 hours (before dinner) after the 2 mg/kg naloxone infusion or placebo. To evaluate possible naloxone-induced physical symptoms that might indirectly mediate effects on appetite or food intake, volunteers also completed at these times a physical symptom checklist.

Statistical analysis of naloxone’s effects on volunteers’ food intake and self-ratings was performed using repeated measures analysis of variance (ANOVAR). For food intake, there were two trial factors, drug (naloxone) and meal. df = 1.6 for these main effects of naloxone and meal as well as the interaction effect, naloxone × meal. For all food intake analyses, i.e., for all calories, or for grams of carbohydrate, protein, or fat, there were no significant main effects for meal or interaction effects for naloxone × meal. Significant main effects for naloxone were confirmed and attributed to meals by the use of appropriate t-tests as well as the generally more conservative nonparametric (np), Wilcoxon matched pairs–signed ranks test (two-tail). Nonsignificance (NS) was set at p > 0.1.

RESULTS

The food intake (calories) of our volunteers was significantly decreased by
naloxone administration (Fig. 1) \( (F = 10.4, p = 0.02) \): the mean ± SEM kilocalories for the group on the naloxone day was 1372 ± 312, compared to 1918 ± 250 on the placebo day, a 28% reduction \( (t = 3.23, p < 0.02; np = p < 0.02) \). All seven volunteers ingested fewer calories during these preselected prepared meals after naloxone than after placebo.

The reduction in food intake was evident at both lunch and dinner. Six of seven volunteers ingested fewer calories at lunch, and six of seven volunteers (1, no difference) ingested fewer calories at dinner during the naloxone than the placebo day. At lunch, 2.75 hours after the naloxone infusion, volunteers consumed 700 ± 156 kcal (mean ± SEM), a reduction of 33% from their intake of 1043 ± 111 on the placebo day \( (t = 1.99, p < 0.1; np = p < 0.05) \). Intake at dinner, 6.75 hours after the naloxone bolus infusion, was a mean ± SEM of 672 ± 166 kcal, a significant reduction of 23% from volunteers’ intake after placebo \( (674 ± 197 \text{ kcal}, t = 3.47, p < 0.02) \).

Analysis of the ingested calories demonstrated significant effects of naloxone in reducing both protein and fat ingestion \( (F = 13.5, p = 0.01, F = 10.5, p = 0.02, \text{ respectively}) \). There was a significant (34%)

---

**Fig. 1.** A comparison of the mean (T = SEM) food intake of seven normal volunteers after intravenous administration of 2 mg/kg naloxone and placebo on separate days in a double-blind, random but balanced cross-over experimental design. Presellected prepared trays were served at 2.75 hours (lunch) and 7.75 hours after the intravenous infusion of naloxone or placebo. Total is the mean (T = SEM) number of calories consumed by the volunteers at both lunch and dinner. \( *p<0.02, *p<0.1, \text{ paired Student } t \text{ test, two-tail} \).

**Fig. 2.** A comparison of the mean (T = SEM) food intake, by type, of seven normal volunteers after intravenous administration of 2 mg/kg naloxone and placebo on separate days in a double-blind, random but balanced cross-over experimental design. Presellected prepared trays were served at 2.75 hours (lunch) and 7.75 hours after infusion of naloxone or placebo. Total is the mean (T = SEM) number of grams consumed by the volunteers at both lunch and dinner. \( *p<0.02, **p<0.05, *p<0.1, \text{ paired Student } t \text{ test, two-tail} \).
NALOXONE REDUCES FOOD INTAKE

TABLE 1. Mean ± SEM (mm) of 7 Normal Volunteers’ Ratings on Analogue Scales of Hunger and Thinking about Food during the Course of their 2 Study Days

<table>
<thead>
<tr>
<th>Substance</th>
<th>Baselinea</th>
<th>0.75 hrb</th>
<th>1.5 hr</th>
<th>4 hr</th>
<th>7 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>33.8 ± 11.4</td>
<td>35.6 ± 11.5</td>
<td>39.9 ± 11.9</td>
<td>4.6 ± 1.9</td>
<td>17.8 ± 8.1</td>
</tr>
<tr>
<td>Naloxone</td>
<td>28.2 ± 10.3</td>
<td>28.7 ± 12.5</td>
<td>32.5 ± 14.5</td>
<td>4.8 ± 1.4</td>
<td>20.1 ± 8.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>23.6 ± 11.7</td>
<td>24.4 ± 12.7</td>
<td>30.2 ± 13.7</td>
<td>3.6 ± 1.3</td>
<td>8.9 ± 3.8</td>
</tr>
<tr>
<td>Naloxone</td>
<td>27.7 ± 10.7</td>
<td>29.2 ± 11.0</td>
<td>40.6 ± 11.3</td>
<td>4.8 ± 1.7</td>
<td>11.7 ± 5.1</td>
</tr>
</tbody>
</table>

Higher numbers represent increased hunger or thinking about food. Maximum score = 100.
aScored by volunteer before naloxone or placebo infusion.
bHours after intravenous infusion of either 2 mg/kg naloxone or placebo. Lunch was at 2.75 hr, dinner at 7.75 hr.

reduction in both total protein and total fat ingested on the naloxone compared to the placebo day, (t-test, p < 0.02 and < 0.05, respectively; np = p < 0.05). Naloxone did not have a significant effect on carbohydrate ingestion (F = 2.3, p = 0.18), although total carbohydrate ingestion was reduced 20% after naloxone compared to placebo (t = 1.52, NS). Nevertheless, six of seven volunteers had decreased carbohydrate ingestion after naloxone compared to placebo (Fig. 2).

Despite this significant effect on food intake, naloxone had no effect on volunteers’ analogue ratings of hunger or thinking about food (Table 1). Consistent with this finding, an equal number of volunteers noted increased appetite on the mood adjective checklist on the placebo and naloxone days. This was also true for notations of decreased appetite on the checklist.

Physical symptoms were rarely noted by volunteers on the symptom checklists. Five volunteers had no somatic complaints, but in the afternoon after the naloxone infusion, one volunteer did note mild nausea and weakness, as well as a strange taste in her mouth; another volunteer noted a mild stomach ache.

DISCUSSION

The results of this study demonstrate that the administration of naloxone, in a dose equivalent to that used in experimental studies with animals, can reduce food intake in humans. These data suggest that blockade of the EOS in normal volunteers can reduce food intake and thus that the EOS is actively involved in the regulation of food intake in humans.

The possibility that the reduced intake of our volunteers was an indirect effect of naloxone-induced mental or physical symptoms seems unlikely but cannot be dismissed with certainty. Clinically apparent mood or physical changes were essentially limited to one volunteer, but all seven volunteers ingested fewer calories after naloxone than after placebo. Nevertheless, it is possible that at this dose of naloxone subtle alterations of mood may occur more consistently in normal volunteers. Mood effects after this dose of naloxone are currently under further investigation and will be reported elsewhere. However, one would have expected nonspecific effects of mental or physical symptoms to be demonstrable in altered perceptions of hunger. This did not occur.
Since the initiation of our study, Thompson et al. (13) have reported that a prolonged intravenous infusion of naloxone over a period of hours (reaching a total dose of 18 mg [0.3 mg/kg]) can reduce the food intake of healthy humans after a 2-deoxy-D-glucose challenge. Consistent with the results of the present study, despite an absence of effect on the subjects' perception of the intensity of 2-deoxy-D-glucose-induced hunger, naloxone was found to produce a 26% reduction in intake.

The EOS is in reality several systems characterized by different concentrations of a variety of endogenous opiates, opiate receptor subtypes, and anatomic locations within the central nervous system (CNS) and periphery with uncertain and unclear interrelations (8,14). This complexity may partially explain the apparent differences in naloxone doses required in humans to effect various behaviors and physiologic changes as well as the apparent lack of correlation within subjects in these effects of naloxone. For example, the dose of naloxone required to produce effects on plasma cortisol levels in normals would seem to be lower than that required to produce effects on blood pressure regulation and mood (9, 10, 15). The results of this study would suggest that the threshold for naloxone’s effects on food intake is lower than the threshold for its effects on mood. Further studies are required to determine the site or sites of action involved in naloxone’s suppression of food intake in humans.

The prolonged effect of naloxone on food intake warrants comment. We have found a similar prolonged effect of high-dose naloxone on other aspects of behavior and mood and have discussed this phenomenon at greater length (10). This long apparent effect suggests that abrupt but nevertheless relatively brief changes in the physiology of the EOS may lead to changes of much longer duration in the organism’s functional state. This finding is consistent with an hypothesized neuromodulatory role for the EOS in the CNS and suggests the possible importance of the EOS in human state changes such as anxiety, depression, obesity, anorexia nervosa, or bulimia.

In recent years, several clinical studies to evaluate the role of the EOS in patients with eating disorders have been done. No change in plasma beta-endorphin levels was found in obese patients during a diet regimen and no difference in plasma beta-endorphin levels was found between obese patients and their normal-weight family members (16). However, cerebrospinal fluid opioid levels, as measured by a radioreceptor assay, perhaps a better reflection of CNS EOS activity, were found to change with nutritional status in patients with anorexia nervosa (17). Pain threshold, hypothesized as a measurement of EOS tone, was found to be decreased in the obese (18), whereas no particular sensitivity to behavioral or physiologic effects of intravenous naloxone administration in doses up to 30 mg/70 kg was found in obese patients in another study (19). The administration of high-dose naloxone to patients should help clarify the relationship between the EOS and the pathogenesis of eating disorders.

The experimental study of the therapeutic potential of high-dose naloxone administration in patients with eating disorders is warranted because these preliminary results suggest that naloxone may reduce food intake in humans without decreasing their satiety. These studies will need to evaluate food intake directly and will not be able to rely solely on self-rat-
NALOXONE REDUCES FOOD INTAKE

ings. However, high-dose naloxone should be administered only with caution under controlled experimental conditions. The relatively lower threshold for naloxone’s effects on food intake is nevertheless near its threshold for mood, blood pressure, and other somatic alterations. None of the subjects in this study had a prolonged clinically significant mood alteration. However, we have had experience with two normal volunteers who, on the evening or the day after administration of naloxone at a dose less than or equal to 2 mg/kg, had the onset of dysphoric states. These were temporary and not severe. However, the presence of an eating disorder or the long-term administration of naloxone could be accompanied by increased susceptibility to this and other effects of high-dose naloxone administration.

The authors are indebted to the Nutrition Department of the Clinical Center, NIH (in particular, Ms. Ernestina Bou and Ms. Mindy L. Lechner), the nursing service of ward 6D of the Clinical Center, and Endo Laboratorities, Inc., for their generous gift of the naloxone (Narcan) used in this study.

REFERENCES

2. Margulis DL: Beta-endorphin and endoloxone: Hormones of the autonomic nervous system for the conservation or expenditure of bodily resources and energy in anticipation of famine or feast. Neurosci Biobehav Rev 3:155–162, 1979

Psychosomatic Medicine Vol. 47, No. 2 (March/April 1985) 137