Satiety Effects of the Type A CCK Receptor Antagonist Loxiglumide in Lean and Obese Women

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Several studies have demonstrated that administration of cholecystokinin (CCK) reduces food intake in several species, including humans. In animal studies CCK-receptor antagonists have been reported to increase food intake, suggesting a physiological satiety effect of CCK in these animals. In a double-blind, placebo-controlled study, we investigated the effect of the specific CCK-A receptor antagonist loxiglumide on food intake (carbohydrate-rich meal) and on subjective hunger feelings scored with visual analogue scales and food selection lists in seven healthy obese women and in seven healthy lean women. Loxiglumide was administered intravenously in a dose of 10 mg/kg ideal weight/h. For the whole group, food intake during loxiglumide (359 ± 39 g) was not significantly different from food intake during saline infusion (333 ± 31 g). Also, when the lean and obese subgroups were analyzed separately, no significant influence of loxiglumide on food intake was found. In addition, no significant differences in satiety scores were seen using the food selection lists or visual analogue scales. In conclusion, in the present study during infusing the CCK-A receptor antagonist loxiglumide we found no increase in preprandial satiety nor in food intake of a carbohydrate-rich meal nor in postprandial satiety in lean and obese women.

Key Words: Cholecystokinin, satiety, obese women, CCK-receptor antagonist, loxiglumide, food intake

Introduction

Cholecystokinin (CCK) was identified from preparations of intestinal extracts by its ability to stimulate gallbladder contraction (Liddle 1989). Several other biological actions of CCK have subsequently been identified, like stimulation of pancreatic exocrine enzyme secretion, inhibition of gastric emptying, influences on intestinal motility, and effects on food intake (Liddle 1989). Several studies have demonstrated that CCK reduces food intake in several species including humans (Linden 1989; Gibbs et al 1973; Bado et al 1988; Gregory et al 1989; Weller et al 1989; Stacher 1986; Pi-Sunyer et al 1982; Kissileff et al 1981; Stacher et al 1982). It is, however, not known whether this satiety effect of CCK is physiological in humans, since plasma CCK levels have not been measured. It is quite possible that in the human studies in which a satiety effect of CCK was demonstrated, plasma CCK levels were in the supraphysiological range. However, in a number of animal species it has been shown that administration of a CCK-A receptor antagonist increases food intake (Silver et al 1989; Reidelberger et al

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1989; Ebenezer et al 1990; Hewson et al 1900; Smith et al 1991; Corwin et al 1991). We have investigated whether the potent and specific CCK-A receptor antagonist loxiglumide (CR1505) (Makovec et al 1985) increases food intake in lean and obese healthy women. If so, this would be an important indication for a physiological satiety effect of CCK in humans.

Materials and Methods

Seven healthy obese women (mean age 43 ± 3 yr, mean body mass index 39 ± 2 kg/m²) and seven healthy lean women (mean age 42 ± 3 yr, mean body mass index 22 ± 0.3 kg/m²) were studied. Informed consent was obtained from all subjects. The protocol had been approved by the local human ethics committee.

After an overnight fast, the volunteers presented at our laboratory at 08.00 h. An intravenous cannula was inserted into the antecubital vein of one arm for infusion of loxiglumide or saline (placebo). Saline or loxiglumide 10 mg/kg ideal weight/h (Rotta Research Laboratories, Monza, Italy) was infused through an intravenous catheter for 165 min, in random order and double blinded. In obese persons the ideal weight was calculated by subtracting 100 from their body length in cm (Broca weight) (Kelke et al 1992), while for lean subjects their actual weight was used. We have shown in previous investigations that this calculation used for the infusion of gastrointestinal hormones such as CCK results in comparable plasma hormone levels between lean and obese subjects (Lieverse et al 1993). The infusions were started at 09.00 h. The two studies were separated from each other by an interval of at least 1 week. The investigations were performed irrespective of the time of the menstrual cycle. Sixty minutes after the start of the saline or loxiglumide infusion, a banana shake consisting of 100 g of bananas (132 kcal), supplemented with water to 300 ml and blended, was served and consumed within 3 minutes. Fifteen minutes later, at time 75 min, a solid meal of banana slices containing 1 g/100 g of protein, 0 g/100 g of fat, and 32 g/100 g of carbohydrates was offered in abundance. The meal was weighed before and after consumption to determine the exact amount of food consumed.

Subjective criteria like the wish to eat, hunger feeling, fullness, and prospective feeding intentions were scored on 100-mm visual analogue scales (Blundell and Burley 1987; Silverstone 1982). These criteria were assessed basally and at 15-min interval until 60 min after the end of the infusion period. The following questions were asked:

How strong is your wish to eat? (from very weak to very strong).
How hungry do you feel? (from not hungry at all to as hungry as I have ever felt).
How full do you feel? (from not full at all to very full).
How much food do you think you could eat? (from nothing to very much).

In addition, the subjects also indicated on visual analogue scales whether they appreciated the meal and whether they experienced nausea. Subjective hunger feelings were also measured with food selection lists, as described by Hill (1987) and modified for Dutch feeding customs. Each food selection list was accompanied by a photograph showing 6 protein-rich, 6 fat-rich, 6 carbohydrate-rich (each about 200 kcal) and 6 low-energy items. For each of these 24 items, the subjects were asked if they wanted to eat the item at that moment and to indicate the amount, double the amount, half the amount, or nothing of the item they wished to consume. Every item was scored independent of the other items. Subjects were presented with a food-selection list 15 min before the infusion, 15 min before the banana shake (at time 45 min), 15 min after the meal (at time 90 min), and at time 120 min, time 165 min (end of the infusion), and time 225 min (end of the experiment). Every time the list was presented, the total amount of caloric items was calculated (half the amount = 1/2 caloric item, double the amount = 2 caloric items).

Statistical Analysis

Results are given as mean ± SEM. Statistical analysis of hunger feelings was performed by calculating the incremental integrated area under the curve (AUC) before and after the meal, followed by Wilcoxon matched pairs signed rank test. Food intake was compared using Wilcoxon matched pairs signed rank test. Differences between lean and obese subjects were analyzed using Mann-Whitney test. The significance level was set at $p < .05$.

Results

For the whole group (obese and lean women together) food intake was not significantly different between the loxiglumide experiment (359±39 g) and the control experiment (333±31 g). Neither was food intake significantly different between the loxiglumide and control experiment in the lean subjects (405 ± 56 g vs. 365 ± 42 g, respectively) nor in the obese subjects (313 ± 54 g vs. 301 ± 45 g, respectively; Figure 1). No significant differences were seen between loxiglumide and saline infusion using the food selection lists or the visual analogue scales (Table 1, Figure 2). Looking at lean and obese subjects separately, there was a decrease in prospective feeding intentions in the lean group during loxiglumide ($p = .028$, Table 1). There was a significant greater postprandial satiety effect ($p < .01$) during loxiglumide in the obese than in the lean individuals for wish to eat ($p = .006$), hunger feelings ($p = .009$), and fullness ($p = .003$) (Table 1). No other significant differences between loxiglumide and saline or between obese and lean subjects were found (Table 1).

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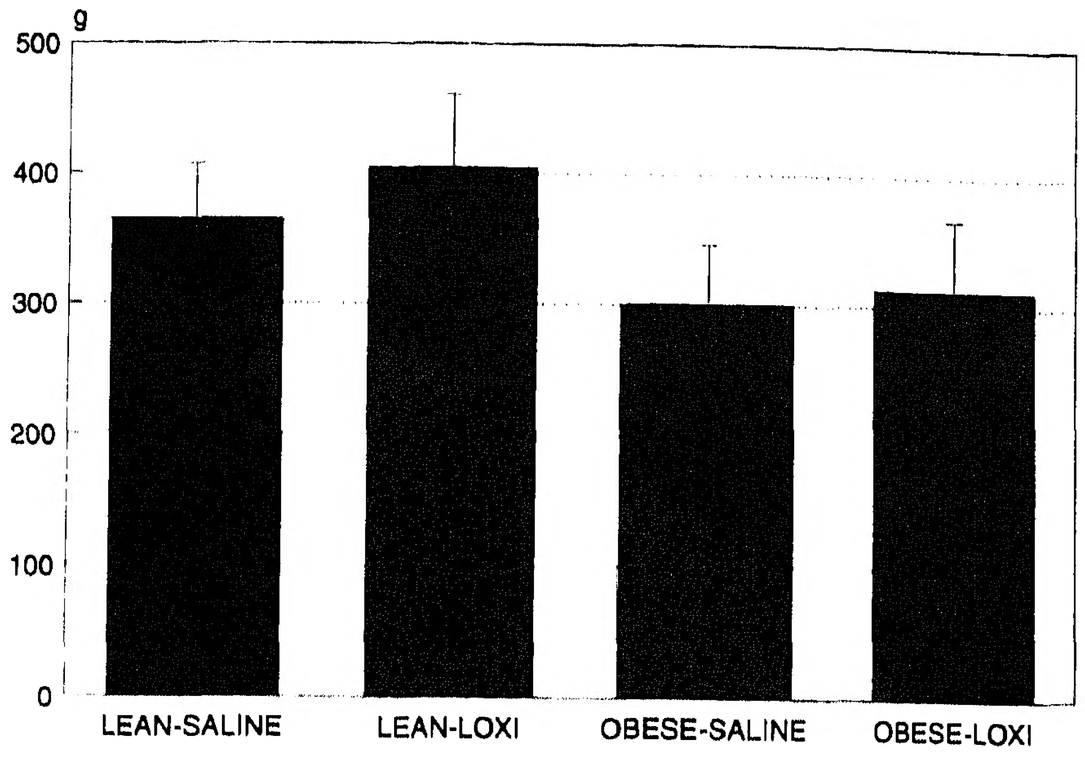

Figure 1. Food intake of a carbohydrate rich meal (mean ± SEM) during saline or loxiglumide (LOXI) infusion (10 mg/kg ideal weight/h) by seven lean and seven obese healthy women.

Both lean and obese subjects liked bananas equally (59 ± 9 and 65 ± 7 mm, respectively, on 100-mm visual analogue scales). The duration of the meal was significantly shorter with loxiglumide (5.1 ± 0.6 min) for obese subjects than during saline (7.3 ± 0.8 min, $p < .05$), whereas lean subjects ate as long during loxiglumide (6.4 ± 0.8 min) as during saline (6.1 ± 0.6 min). No nausea during any study was recorded in lean or obese subjects.

Discussion

In contrast to studies in several animal species, we did not observe a significant increase in food intake during administration of the potent and specific CCK-A receptor antagonist loxiglumide in humans. Neither in the obese nor in the lean women was there a significant difference in food intake between the loxiglumide and the control experiment. In addition, we found no increase in preprandial or postprandial subjective hunger feelings during loxiglumide administration compared to placebo.

Recently, Wolkowitz et al observed in eight healthy male volunteers a significant increase in hunger feelings with MK-329, another CCK-A antagonist (Wolkowitz et al 1990), whereas we found no significant increase in hunger sensations. The cause of this difference is not apparent, but it may be related to differences in study protocols. First, in the study of Wolkowitz et al the CCK-A receptor antagonist was administered orally, whereas in our study the CCK-A

Table 1. Incremental Areas under the Curve (mean ± SEM) for Different Satiety Parameters Preprandially (during 60 min) and Postprandially (during 135 min) with Saline or Loxiglumide (10 mg/kg ideal weight/h) Infusion

	All ($n = 14$)	Lean ($n = 7$)	Obese ($n = 7$)	p (lean vs. obese)
Wish to eat				
preprandial saline	133 ± 118	182 ± 217	84 ± 112	NS*
preprandial loxiglumide	245 ± 188	247 ± 363	242 ± 148	NS
p (saline vs. loxiglumide)	NS	NS	NS	
postprandial saline	1402 ± 363	1659 ± 400	1145 ± 624	NS
postprandial loxiglumide	962 ± 489	1988 ± 619	−63 ± 551	0.006
p (saline vs. loxiglumide)	NS	NS	NS	
Hunger				
preprandial saline	160 ± 130	197 ± 197	122 ± 186	NS
preprandial loxiglumide	103 ± 172	−103 ± 295	309 ± 165	NS
p (saline vs. loxiglumide)	NS	NS	0.091	
postprandial saline	1355 ± 307	1831 ± 433	879 ± 371	0.084
postprandial loxiglumide	850 ± 419	1768 ± 455	−69 ± 523	0.009
p (saline vs. loxiglumide)	NS	NS	NS	
Fullness				
preprandial saline	−92 ± 117	−220 ± 189	35 ± 134	NS
preprandial loxiglumide	−80 ± 114	−135 ± 219	−25 ± 85	NS
p (saline vs. loxiglumide)	NS	NS	NS	
postprandial saline	−1452 ± 497	−1737 ± 962	−1169 ± 346	NS
postprandial loxiglumide	−1109 ± 537	−2464 ± 566	246 ± 564	0.003
p (saline vs. loxiglumide)	NS	NS	NS	
Prospective feeding				
preprandial saline	277 ± 156	496 ± 282	59 ± 100	NS
preprandial loxiglumide	−100 ± 97	−271 ± 108	70 ± 140	0.064
p (saline vs. loxiglumide)	NS	0.028	NS	
postprandial saline	1381 ± 382	1459 ± 570	1302 ± 552	NS
postprandial loxiglumide	1122 ± 361	1697 ± 607	546 ± 291	0.084
p (saline vs. loxiglumide)	NS	NS	0.091	

*p values > 0.10 are given as NS.

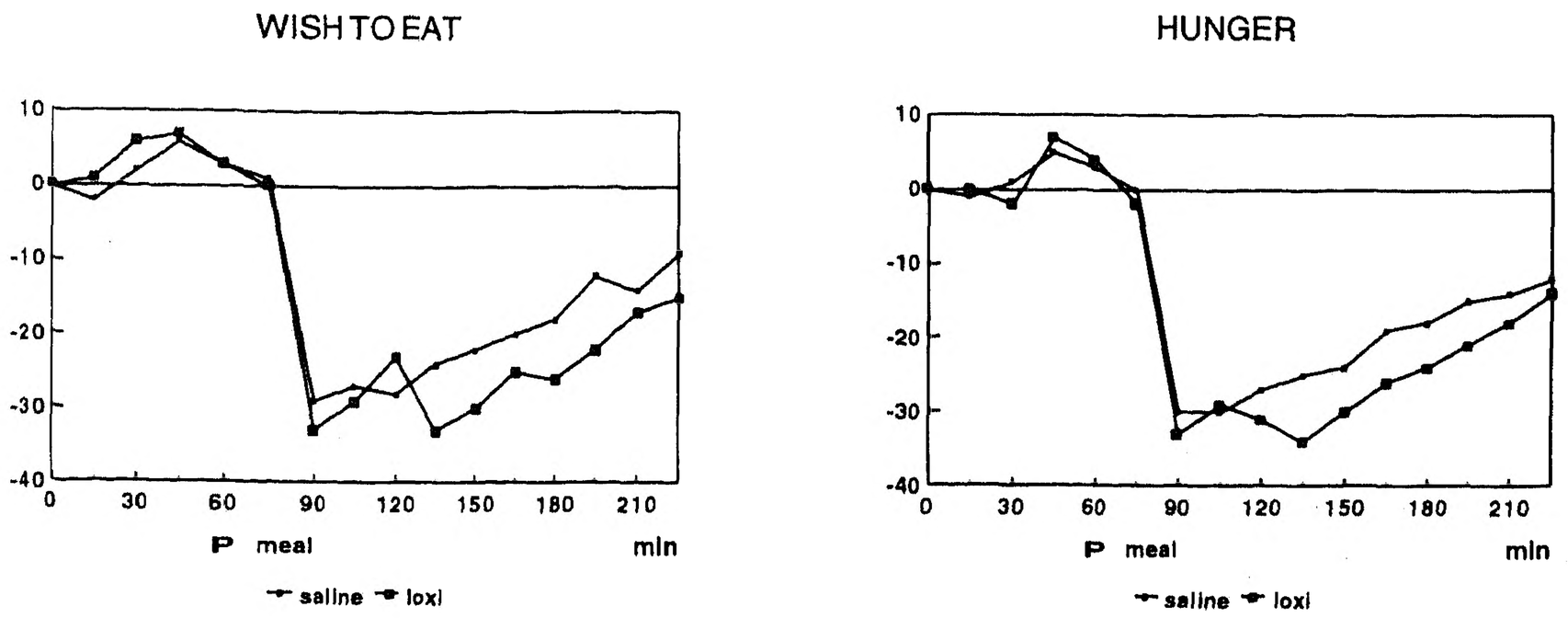

Figure 2. Food intake. Satiety parameters such as wish to eat, hunger, fullness, and prospective feeding intentions scored on visual analogue scales during loxiglumide (Loxi, 10 mg/kg ideal body weight/h) infusion from time 0 min to time 165 min in 14 healthy women (seven lean women, seven obese women). Satiety scores are expressed in percentual changes considering the start of loxiglumide infusion time (0 min) as a reference point. At time 60 min, a banana shake (p = preload) was ingested; at time 75 min a carbohydrate-rich meal was consumed until satiation.

receptor antagonist was administered by continuous intravenous infusion. Previous studies have shown that the dose of loxiglumide we infused completely inhibits pancreatic enzyme secretion and gallbladder contraction in response to exogenous CCK (Schmidt et al 1991). Second, in the study of Wolkowitz et al, the subjects scored their first visual analogue scale as early as 5.45 h AM, ingested MK-329 orally, and 90 min later scored their second visual analogue scale. In our study, which started at 8.00 h AM, the mean of 5 visual analogue scales was used for the basal hunger score and hunger feelings were scored every 15 minutes during intravenous administration of the CCK-receptor antagonist loxiglumide. Sixty minutes after the start of the loxiglumide infusion, a banana shake was consumed. Third, Wolkowitz et al investigated male volunteers, whereas we investigated female subjects.

The results of our study are in agreement with those of Drewe et al (1992), who found no influence of loxiglumide on hunger feelings or food intake in lean, healthy subjects. That study, however, was performed with an intraduodenal tube in situ; it cannot be excluded that the duodenal intubation may have adversely affected the results. A more likely explanation for the fact that we did not observe a significant increase in food intake or in postprandial hunger feelings during loxiglumide administration may be related to the composition of the meal. In our study we offered a carbohydrate-rich meal that does not release endogenous CCK. It is well known that fat and protein, but not carbohydrates, are potent stimuli of CCK secretion. It therefore remains possible that blockade of CCK-A receptors increases food intake when a protein or fat meal, which induces CCK release, is consumed. In further studies evaluating the effect of CCK-

A receptor blockade on food intake in humans, special attention should be drawn to the composition of the meal.

The decrease in preprandial prospective feeding intentions in lean subjects was the only effect of loxiglumide found to be significant ($p = .028$), but it is probably of no importance because it was not associated with increases in hunger scores, wish to eat, or a decrease in feelings of fullness.

A remarkable finding of this study was the significantly stronger postprandial satiety effect during loxiglumide infusion in obese as compared to lean individuals. This difference in postprandial satiety was present for wish to eat, hunger, and fullness (each $p < .01$), and there was a trend towards statistical significance for prospective feeding intentions. These results suggest that differences exist in postprandial satiety between lean and obese subjects; however, an explanation for this observation is not readily available.

Conclusion

In conclusion, in the present study we found no significant increase in preprandial satiety nor in food intake of a carbohydrate-rich meal or in postprandial satiety with the CCK-A receptor antagonist loxiglumide in lean and obese women.

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