Loxiglumide, a CCK-A receptor antagonist, stimulates calorie intake and hunger feelings in humans

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Loxiglumide, a CCK-A receptor antagonist, stimulates calorie intake and hunger feelings in humans. Am J Physiol Regulatory Integrative Comp Physiol 280: R1149–R1154, 2001.—Exogenous cholecystokinin (CCK) induces early satiety when infused into humans. Whether alimentary CCK (CCK-A) receptor blockade stimulates food intake in humans is, however, uncertain. The aim of the present investigation was, therefore, to establish the effect of CCK-A receptor blockade on satiety and eating behavior in healthy volunteers. To further explore the role of endogenous CCK, the effects of the specific CCK-A receptor antagonist loxiglumide (Lox; 22 µmol·kg⁻¹·h⁻¹) on satiety and eating behavior were investigated in healthy men and compared with saline infusions (as placebo) in a series of randomized, double-blind, placebo-controlled, crossover studies. Lox produced a slight (7%), but not significant (P = 0.104), increase in food intake that was accompanied by a modest (10%), but significant (P < 0.004), increase in calorie intake. Fluid ingestion was not affected by Lox. Subjects experienced more hunger and delayed fullness during Lox infusion than during saline infusion (P < 0.05). This study provides further evidence that CCK is an endogenous physiological satiety signal acting through CCK-A receptor-mediated mechanisms. Repeated-dose studies comparing hunger and satiety responses after CCK-A receptor blockade in healthy subjects and patients with eating disorders may help clarify the possible involvement of endogenous CCK in these conditions.

cholecystokinin; appetite; eating behavior

THE REGULATION OF FOOD INTAKE and satiety is complex. Only insufficient information is available about the mechanisms and processes that control short-term satiety in humans: on the basis of animal trials, it is assumed that food intake is suppressed on stimulation of specific receptors within the gastrointestinal tract (13, 59, 62). Accordingly, the role of nutrient-stimulated, meal-ending satiation has been extensively explored (2, 3, 9). Along these lines of investigation, it has been suggested that gastrointestinal peptides participate in the regulation of nutrient-stimulated inhibition of food intake. Experimental evidence, largely based on studies with exogenous peptide administration, has been provided to support a role as a satiety factor for the brain-gut peptides cholecystokinin (CCK), gastrin-releasing peptide/bombesin, and glucagon-like peptide-1 (GLP-1), all of which have been shown to reduce meal size and energy intake in healthy human subjects (14, 15, 19, 20, 27, 52). These results suggest that these peptides might be involved in the physiological control of food intake.

CCK is the first gut-born peptide candidate for a physiological role in regulating food intake in animals and humans (6, 16, 26, 33, 37, 54–56, 63, 65). CCK is normally released from endocrine cells of the duodenum and jejunum, contingent on intraluminal fat or amino acids (30, 31). In addition to stimulation of gallbladder contraction and exocrine pancreatic secretion, exogenous CCK causes a delay in gastric emptying and, as mentioned previously, inhibition of food intake (29, 32). Information primarily obtained in animals, using specific alimentary CCK (CCK-A) receptor antagonists, indicates that the CCK-induced satiation signals are mediated via peripheral CCK-A receptors, thereby implying a physiological role for endogenous CCK (1, 4, 41, 42, 48, 58, 67).

Moran and co-workers (44) recently provided additional experimental evidence in support of the hypothesis that rats that do not express CCK-A receptors develop obesity, hyperglycemia, and non-insulin-dependent diabetes mellitus; in short-term feeding trials, the animals were completely resistant to exogenous CCK administration. In 24-h solid food access trials, the rats consumed significantly more food than control animals. These results are consistent with the hypothesis that the lack of CCK-A receptors results in a deficit of satiety signaling, leading to increases in meal size, overall hyperphagia, and obesity. The availability of potent and selective CCK-A receptor antagonists has made it possible to continue these investigations. Loxiglumide (Lox) is one of these specific antagonists available for human use (26–29). Lox, therefore, appeared
to be a useful tool to test the hypothesis that endogenous CCK is a physiological satiety signal in humans.

MATERIALS AND METHODS

Subjects and study design. Forty healthy male subjects aged 21–34 yr were studied using a randomized, double-blind, crossover design. The weight of all subjects was within normal range considering their age, gender, and height. Each subject gave informed consent for the study. The protocols were approved by the Human Ethical Research Committee of the University Hospital of Basel. Before acceptance, each participant was required to complete a medical interview, undergo a full physical examination, and participate in an initial laboratory screening. No subject was taking any medication or had a history of food allergies or dietary restrictions.

Protocol. Two tests, in random order but separated by ≥7 days, were performed in each subject. The tests were identical in design (Fig. 1), except for the intravenous infusion (saline or Lox). An identical standard meal was presented to the subjects on each occasion, and the order of the studies was randomized. The meal consisted of 1) orange juice as an appetizer (480 kcal/l), 2) small ham sandwiches (60 g bread, 10 g butter, and 25 g ham; 305 kcal/sandwich) and more orange juice or plain water, 3) chocolate mousse (100 kcal/100 g), and 4) coffee with cream (12 g cream = 20 kcal) and sugar (optional, 4.5 g sugar = 18 kcal). Each subject was free to eat and drink as much as he wished, but the order of food intake had to follow the above schedule. To reduce participants’ awareness of the amount of food being provided, food was served in excess. No additional food or beverage was allowed during the test. Food intake was measured by absolute food and fluid weight, from which the total calorie ingestion was calculated. The time taken to complete the meal was also measured.

On the study day, each subject ate breakfast if this was his normal custom, but no food was allowed after 8 AM. At 12 noon, an intravenous infusion of saline or Lox (22 μmol·kg⁻¹·h⁻¹) was started and continued for the duration of the test (6, 23, 24). The dose of Lox was chosen from previous experiments (6, 23, 24) in which 22 μmol·kg⁻¹·h⁻¹ was documented as the most effective dose with respect to antagonizing CCK-stimulated effects. Infusions were delivered by ambulatory pumps through a Teflon catheter inserted into a forearm vein. Participants were able to sit, eat, and walk comfortably while receiving the infusion. Sixty minutes after the start of the infusion, the test meal was presented, and each participant was invited to eat and drink as much as he wished.

Starting at 12 noon, subjects scored their subjective feelings of hunger and fullness at 15-min intervals throughout the tests using a visual analog scale from 0 to 10 and indicated their score on a questionnaire. The scale and score have previously been described (67, 68). For example, a score of 0 for hunger indicated that the subject was not hungry at all, 2 indicated slightly hungry, 5 indicated moderately hungry, 8 indicated very hungry, and 10 indicated absolutely ravenous. Adverse events were assessed by the attending physician through close observation of each subject; in addition, each participant was questioned after each test and after he had completed all tests whether or not he had experienced any adverse effects.

Infusions. Lox infusions were prepared from freeze-dried synthetic powder obtained as a gift from Rotta Research Laboratorium. The solutions were prepared by the University of Basel Hospital Pharmacy under aseptic conditions. The Lox solutions were indistinguishable in appearance from the control (placebo) saline solution, and the investigator conducting the studies was unaware of the respective treatment, thereby making it possible to deliver treatments in a double-blind fashion.

Statistical analysis. Values are means ± SE. The amount of food eaten and drunk and the corresponding energy intake were compared by a paired t-test. Scores for hunger and fullness were compared at the different time points before and after the meal between the two treatments using multiple paired t-tests with Bonferroni correction for multiple comparisons as appropriate (59, 60). P < 0.05 was accepted as significant difference.

RESULTS

Food intake. Intravenous Lox induced a slight (7%), but not significant (P = 0.104), increase in the amount of food eaten that was accompanied by a modest (10%), but significant (P = 0.004), increase in calorie consumption (Table 1). Total fluid intake was not changed by intravenous Lox. Meal durations were similar in the two treatments and did not show any significant differences (data not shown). None of the participants reported any abdominal discomfort or side effects during any treatment. Furthermore, when questioned at the end of each test, none of the subjects reported any adverse reaction.

Eating behavior. Baseline hunger and satiety ratings were similar between the two treatment conditions (Fig. 2). Hunger ratings [postdrug ratings − baseline (predrug) ratings] were higher (P < 0.05) during Lox infusion than with placebo at 60 min (immediately before starting meal intake). The difference persisted in the first 45 min after food ingestion was started (Fig. 2)

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<th>Table 1. Effect of Lox on food-related parameters in healthy subjects</th>
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P = 0.104,
2). Ratings of satiety were, however, not significantly different in the premeal period. After food ingestion, a reduced feeling of fullness was observed with Lox infusion at 15 min after meal intake was started (P, 0.05).

DISCUSSION

This study has documented in healthy male subjects 1) a small, but significant, increase in calorie intake and 2) a significant increase in subjective hunger ratings produced by the acute administration of Lox, a specific CCK-A receptor antagonist that is devoid of any intrinsic activity. We interpret these results as compelling evidence that endogenous CCK released by food ingestion physiologically curtails hunger feelings and induces early satiety in healthy male volunteers.

The results imply that CCK is one of several physiological satiety signals in humans.

We and others have reported elsewhere (6, 26, 34, 35, 37, 49) that infusion of exogenous CCK inhibits food intake and induces early satiety when the peptide is given shortly before meal ingestion. Along the same lines of investigation, intraduodenal administration of fat or digestion products of fat reduces food intake and stimulates subjective feelings of fullness (6, 36, 40, 69, 70). Digestion products of fat are potent stimulants of plasma CCK release (30); therefore, fat-induced satiety effects are associated with plasma CCK release. The specific CCK-A receptor antagonist Lox is able to prevent the satiety effects induced by intraduodenal fat (36, 40), implying that endogenous CCK is the mediator of this action. Here we extend these observations by documenting that Lox alone stimulates calorie intake and increases feelings of hunger in healthy male subjects.

Surprisingly, LOX did not significantly increase the amount of food eaten (7% increase vs. controls). This finding could be associated with different mechanisms: 1) the selection of healthy male subjects, 2) the rate of gastric emptying of solids and liquids, and 3) the relative ability of macronutrients to stimulate CCK release. First, the design of the study (only a light breakfast before 8 AM, with no snacks allowed thereafter) and the selection of young male subjects who knew that they were getting a free lunch on test days might be reasons for an unusually high lunch intake, even in the absence of Lox (mean calorie intake 1,689 kcal on the control day). This high degree of baseline food intake may reduce the likelihood that Lox would stimulate further eating. Second, Lox has been shown to accelerate gastric emptying of fatty liquid meals (12); whether Lox also accelerates the solid phase of meals is uncertain. The rate of gastric emptying is, however, an important variable in the regulation of food intake (27, 45, 61). Finally, the test meal contained only limited amounts of fat and protein, both potent secretagogues of CCK release. This may again reduce the likelihood that Lox would stimulate further feeding.

On the basis of reports in animals of short-term inhibition of food intake with exogenous CCK and increased feeding in response to CCK-A receptor blockade, there has been speculation regarding the role of endogenous CCK in the maintenance of body weight (4, 9–11, 62, 71). In the results summarized here, we have seen that intravenous administration of Lox induced a modest, albeit significant, increase in feeding, providing compelling physiological evidence that endogenous CCK is indeed involved in the control of short-term satiety. CCK may interact with other gastrointestinal signals that may influence food intake. Among those signals, several hormones have been proposed to act as satiety factors; these include gastrin-releasing peptide, GLP-1, and peptide YY (8, 18–20, 33, 68). Thus it has been shown that GLP-1 and peptide YY, which are released synchronously from the distal small intestine, have inhibitory effects on food intake and gastric emptying (17, 21, 22, 25, 51). An interaction between CCK and other gastrointestinal hormones released in response to meal ingestion, therefore, seems to be a fruitful line for further investigations.

What is the mechanism of action? CCK can cause inhibitory effects on gastric emptying under certain conditions (12). Presumably, inhibition of gastric emp
tying may in itself cause a limitation of food intake through neural or endocrine signaling pathways, perhaps associated with distension of the stomach (7, 45, 46, 49, 50). A series of studies related to the inhibitory effects of CCK on food intake in rats has suggested that the satiety effects involve the vagus nerve and that the peripheral effects of CCK were transmitted by afferent vagal fibers (43, 47, 53, 56, 66) reaching the brain. Thus it remains most likely that CCK exerts its effects via interaction with sensory nerve fibers in the periphery.

Is there a therapeutic application for CCK-A receptor antagonists in eating disorders? The rationale for the use of CCK-A receptor antagonists in several gastrointestinal disorders has been clearly established (5). Our present study has shown that CCK-A receptor blockade affects short-term satiety. This raises the question of whether the effects produced by Lox can be translated into a therapeutic strategy to modulate body weight. A recent study using CCK-A receptor−/− mice has documented, however, that endogenous CCK mediates inhibition of food intake yet is not essential for the maintenance of body weight (28). These results, along with other data, suggest that CCK is indeed involved in the physiological control of short-term satiety, but not necessarily in the regulation of body weight.

In conclusion, this study has shown that it is possible in the short term to stimulate calorie intake in humans by blocking CCK-A receptors. The mechanism most likely involves inhibition of CCK-A receptors on gastric afferent vagal fibers (46, 47, 56, 66). The findings are in accordance with CCK being a physiological satiety factor.

Perspectives

In the past three decades, the role of preabsorptive factors in regulating food intake and satiety has been one of the major focuses in the field. CCK is one of these preabsorptive factors involved in this regulation.

The present study illustrates that blockade of CCK-A receptors through the specific inhibitor Lox stimulates appetite and calorie intake, supporting the hypothesis that CCK is a physiological satiety factor.

The evidence for CCK as a satiety factor comes from studies that have investigated short-term control of satiety, but we lack good data from humans that support the notion that CCK is a control factor in the regulation of body weight. On the basis of the present evidence, we suggest that appetite-reducing properties of CCK should be further investigated. At this stage, it is premature to predict the long-term effects of CCK on body weight control given the complexity of neurohormonal signals that regulate body weight. Two recent studies in rats suggest, however, that CCK interacts with leptin to produce weight loss (38, 39). The synergistic effect of the leptin- CCK combination on body weight loss depends on the peripheral action of CCK and a central action of leptin. These data would suggest a previously unsuspected role for CCK in body weight regulation that may not depend entirely on reduction of food intake (39). The data imply that a strategy should be developed that enhances the effects of leptin in leptin-resistant obese individuals. The role of CCK in regulating food intake and satiety and, perhaps, body weight control deserves further investigation.

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