Appetite, 1985, *6*, 21–24

Intramuscular Ceruletide Does Not Affect Food Intake in Obese and Non-obese Human Subjects

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Intramuscular ceruletide or placebo was given in a randomized double-blind crossover design to 12 non-obese and 12 obese individuals, 30 min before a palatable lunch meal. No significant effects were found on the amount of food intake or the hunger ratings in any group. Although rapid CCK or ceruletide infusions have been found in some studies to reduce food intake in man and animals, slow infusions have increased food intake. Under the present study conditions, the moderate rate of release of ceruletide from intramuscular depots did not affect the food intake.

A great number of factors regulate food intake. Some of them have immediate effects on satiety, whereas others affect hunger, appetite and satiety on a long-term basis. Cholecystokinin (CCK) has for more than 10 years been a candidate for the short-term control of energy intake. The results of studies with this agent, however, have not been consistent. Although a bolus intravenous injection of CCK was found to reduce food intake, a slow intravenous CCK infusion in fact increased food intake (Sturdevant & Goetz, 1976).

Since native CCK preparations have been difficult to obtain in pure form, a number of studies have been made with CCK octapeptide or the decapeptide ceruletide (caerulein), which both seem to be similar to CCK in action and potency (Ganzina & Santamaria, 1976).

Previous studies with CCK analogues in man have been performed with intravenous infusions and injections. Since the mode of administration of the analogue seems to be of importance for the outcome, we decided to perform a pilot study of the effects of an intramuscular ceruletide injection on food intake and hunger ratings in both non-obese and obese individuals.

Methods

Subjects

Twelve non-obese healthy staff members were invited to participate in the study. From the obesity unit in the Karolinska Hospital, 12 obese patients were recruited. They were invited to participate while they were still on the waiting list to the day-care ward and were weight-stable throughout the study. No subject in the non-obese group was on continuous medication, whereas five obese patients were on medication, which

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remained unchanged throughout the study (antihypertensive and antiphlogistic drugs). Pertinent clinical data are summarized in Table 1. The study was approved by the Ethical Committee of the Karolinska Hospital. All participants were given a detailed written description of the study before entry.

TABLE 1
Clinical characteristics of the subjects

Group	*Ns*			Age (years)	Broca index [kg/(cm − 100)]	Body weight (kg)
	Total	Males	Smokers			
Non-obese	12	5	6	36 (23–57)	0·88 (0·78–0·97)	65·8 (50–89)
Obese	12	2	4	47 (24–62)	1·55 (1·31–1·82)	108·6 (80–120)

Note: Means and ranges (in parentheses) are shown.

Procedure

Each subject participated in two food intake measurements after preadministration of ceruletide or placebo in a double-blind design. Ceruletide and corresponding placebo (lactose) vials were generously supplied by Farmitalia Carlo Erba, Sweden. The interval between the two study occasions ranged from 7 to 14 days. All participants fasted from midnight. At 0815 hrs, they were given a light standard breakfast consisting of two slices of bread and butter with either cheese or ham, one glass of orange juice and one cup of tea or coffee (1520 kJ = 360 kcal). No further intake of food was permitted during the morning. After breakfast, the participants were allowed to read or to perform ordinary work. No strenuous activities were permitted. At 1145 hrs, they returned and were given a deep intramuscular injection in the gluteal region of either ceruletide or placebo. The non-obese group received a standard dose of 10 μg, the obese group a dose of 0·1 μg/kg body-weight but not above a maximum dose of 10 μg. For the non-obese subjects this led to ceruletide doses ranging from 0·11 to 0·20 μg/kg body-weight; for the obese patients, the corresponding figures were 0·083–0·117 μg/kg body-weight.

Immediately before the injection, hunger ratings were performed on horizontal 100 mm visual analogue scales (Bond & Lader, 1974), labelled "not at all hungry" and "very, very hungry" at either end.

At 1215 hrs, the hunger ratings were repeated and a standardized lunch was served. This consisted of a cheese sandwich (737 kJ = 176 kcal), which the participants were instructed always to eat, and a creamy mushroom soup (energy content 7·70 MJ/l = 1·83 Mcal/l). Each subject received his or her soup in identical 1 l containers with a double bottom. This made it impossible to empty the container completely or to estimate the amount of soup poured out. The soup was served in plates of varying shapes and sizes. Thus it was impossible for any individual to compare objectively the amount of soup eaten on each occasion. The subjects were instructed to eat in a relaxed way until they reached a pleasant degree of fullness. When they returned for the second part of the study, this was carried out under identical circumstances, but the alternative drug was injected.

Results

None of the 24 participants dropped out from the study. Twenty-three out of the 24 participants described the soup as 'very tasty". Six of the participants reported very slight side-effects during ceruletide and three during placebo treatment. These side-effects were mainly described as a tendency to flush, dryness of the mouth and slight nausea.

The intakes of soup in the two groups are summarized in Table 2. In either of the groups were there any significant differences between the ceruletide and the placebo meals. The obese subjects ate about 75 g less soup than the non-obese. There were no systematic differences in eating patterns between smokers and non-smokers.

The changes in hunger ratings between the time of the injection and the onset of the meal are shown in Table 2. At the time of the injection, the mean hunger ratings in all four study situations were almost identical (47·6–49·9 mm from the "not at all hungry" end of the analogue line). No systematic changes in hunger feelings between placebo and ceruletide injections were noted in the non-obese or obese groups.

TABLE 2

Soup consumption and hunger rating changes after intramuscular ceruletide or placebo injections

		Intake (g)		Hunger ratings		
Group	Drug	*M*	*SD*	Decreased	Unchanged	Increased
Non-obese	Placebo	332	127	6	3	3
	Ceruletide	315	192	9	1	2
Obese	Placebo	246	117	7	1	4
	Ceruletide	249	100	5	0	7

Note: There are no significant differences in any group.

Discussion

This pilot study failed to demonstrate that an intramuscular injection of ceruletide affects the size of a meal taken 30 min after injection. The double-blind crossover design should make it possible to identify major effects of ceruletide on food intake. We have previously used the same design in a study of the effects of an oral glycerol preload on the subsequent intake of soup and were able to show that glycerol led to a significant 10% reduction of the size of a similar meal (Björvell & Rössner, 1982).

The ceruletide doses were chosen to be effective on gallbladder emptying but without side-effects, in order to prevent any reduction of food intake as a result of nausea. In studies of gallbladder emptying after ceruletide administration (0·3 μg/kg body-weight, i.m.), a substantial reduction of gallbladder area during oral cholecystography was noted from 20 min up to 1 h. With this dose, which was two to three times higher than the one used in our study, mild side-effects were noted in about 60% of the cases (Davidsen & Jörgensen, 1981).

Since no assays are available at present, we were unable to measure circulating ceruletide levels. Furthermore, the concentrations in the central nervous system or in the gastro-intestinal tract at the onset of the meal 30 min after the deep intramuscular

injection are unknown. The half-life of ceruletide is less than 10 min and differences in resorption from the intramuscular site of injection might therefore have led to a considerable degree of variation in ceruletide concentrations at the onset of the meal. However, the fact that subjects reported slight side-effects before the onset of the meal more often after ceruletide may be an indirect indication that the circulating ceruletide levels at that time were in the upper physiological range.

Some studies indicate that CCK, CCK octapeptide or ceruletide injections or infusions may decrease the intake of liquid and solid food in both lean and obese man (Kissileff, Pi-Sunyer, Thornton & Smith, 1981; Pi-Sunyer, Kissileff, Thornton & Smith, 1982; Stacher, Bauer & Steinringer, 1979; Stacher, Steinringer, Schmierer, Schneider & Winklehner, 1982 a, 1982 b). Although statistically significant, these reductions in food intake were very small. A rapid intravenous injection of CCK resulted in a dose-dependent reduction of food intake in rabbit (Houpt, Anika & Wolff, 1978) and in man (Sturdevant & Goetz, 1976). Sturdevant also found that in man, whereas a *rapid* ceruletide injection reduced food intake, a *slow* CCK infusion stimulated food intake. Mendel, Sturdevant and Elashoff (1980) demonstrated that food intake was stimulated dose-dependently by ceruletide infusions in cats. It is therefore possible that the conditions of our study led to an "intermediate" rate of ceruletide release from the intramuscular sites that did not affect food intake in man.

Finally, it should be noted that, whereas the soup our subjects were given was rated as "very tasty", the food used in some of the studies showing an effect of CCK analogues on intake was less palatable. This could explain the discrepancy between our results and those showing an effect of CCK analogues.

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Received 10 July, 1984; revised form 26 September, 1984