

Meal size, satiety and cholecystokinin in gastrectomized humans

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Abstract

A wealth of data supports the idea that the stomach and cholecystokinin octapeptide (CCK-8) normally play important roles in meal size and satiety. We studied long-term gastrectomized humans to further evaluate this possibility. Ten humans, who were gastrectomized 8 (3–12) years earlier, and eight controls ate a meal from a plate placed on a scale connected to a computer and estimated their satiety every minute using a computerized rating scale. Blood levels of CCK-8 were measured before and after the meal. There was no difference between the groups in the amount of food consumed or in the perception of satiety during the meal. Gastrectomized humans had higher blood levels of CCK-8 than controls before the meal; the levels increased after the meal in the controls but not in the gastrectomized subjects. It is suggested that although the stomach and CCK-8 normally are involved in the control of meal size and satiety, their roles are dispensable.

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1. Introduction

There is extensive experimental support for the hypothesis that the stomach plays an important role in the termination of food intake, i.e., satiety [8,32]. Animals with open gastric fistulas, which prevent food from filling the gastrointestinal tract, overeat but will stop eating if the food is allowed to accumulate in the stomach and duodenum [28], and distention of the stomach causes satiety in animals [8,32] and man [25].

Food intake causes release of peptides [12] which mediate satiety by activating tension receptors in the stomach and duodenum [5] and vagal afferents [26]. Many of the effects of peptides on satiety parallel those on gastric emptying and intestinal motility. Thus, out of the peptides which are present in the gastrointestinal tract [7], some facilitate [10,18] and others inhibit [13,34,35] gastric emptying, intestinal motility and food intake [12]. Release of cholecystokinin octapeptide (CCK-8) is believed to be of particular importance [15,27,33]. Thus, CCK-8 can act on receptors localized on the pylorus and gastric wall [20] to affect the rate of gastric emptying [31], and there is a

correlation, although not a proven causal relationship, between the effects of CCK on gastric emptying and satiety. A recent study on the rat, however, suggested that the inhibitory effect of gastrectomy on food intake in part was mediated by an increase in endogenous CCK levels [41]. Here, we report a study on gastrectomized humans, who lack the possible substrate for CCK-8-induced satiety to further examine the role of the stomach in food intake.

2. Methods

2.1. Subjects

Four women and six men aged 62.9 (48–84) (mean, range) years, who had undergone total gastrectomy for gastric cancer 8 (3–12) years earlier were studied. They were operated on at the Department of Surgery, Huddinge University Hospital. The surgical procedure and clinical outcome has been described by others [40]. The patients were the 30% who survive their cancer for more than 3 years and they were free from signs of recurrent disease. Their body mass index (BMI) was 21.6 (17.3–25.0) kg/m² at the time of testing. There were no differences between women and men, and none had a history of gastrointestinal problems or discomfort. Eight healthy volunteers, five women and three men, were studied for

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comparison. They were selected out of a larger group that was studied to obtain data on normal eating behavior and satiety. They were comparable with regard to BMI [24.3 (17.4–32.0) kg/m²] but were somewhat younger [56.0 (46–71) years]. The reason for this difference, which is not statistically significant, is that it was difficult to recruit old subjects. However, the slight difference in age is probably of no importance, because there is no correlation between food intake and age in subjects more than 40 years old (Bergh et al., unpublished results on 18 men and 21 women).

The study was approved by the Ethics Committee of the Karolinska Institutet.

2.2. Behavioral tests

The subjects were instructed to follow their normal breakfast procedures. They came to the laboratory 2 h before testing. They were served fish and potatoes (320 kJ, 6.5 g protein, 7.0 g carbohydrate and 2.5 g fat/100 g; Findus, Bjuv, Sweden) between 11:00 a.m. and 1:00 p.m. The food conformed to their diet habits and they made the choice out of other options (meat dishes of approximately the same caloric density). They served themselves on a plate placed on a balance, which was lowered on the surface of a table. They were allowed to eat as much/as little as they chose to do. The balance was connected to a computer that recorded the weight loss of the plate during the meal. At 1-min intervals, the subject was asked to estimate her/his satiety on a scale ranging from 0 to 10 which appeared on a monitor [1]. The computer stored the satiety ratings. This device, Mandometer, allows simultaneous recording of food intake and satiety.

Before and after the meal, all subjects were asked to estimate the thought of eating on a continuum from very repulsive (0) to very tempting (10) and their feeling of hunger on a continuum from not hungry at all (0) to very hungry (10). Subjects indicated their estimation by making a mark on a 10-cm-long analogue scale and the value was recorded as the closest 0.5 cm.

2.3. Assay of CCK-8

A blood sample was taken from each subject before and after the meal, and the sample was immediately centrifuged and the plasma was stored at -70°C until analyzed for CCK-8 using a previously described method [24].

2.4. Data analysis

In the descriptive statistics in the Subjects section above, ranges were used to show minima and maxima. There were no differences between men and women and the results were therefore combined. The amount of food consumed, the duration of the meal, the level of satiety, the thought of eating, the feeling of hunger and plasma levels of CCK-8

are expressed as means \pm S.E. Between-group comparisons were made with the Mann–Whitney *U* test, and within-group comparisons were made with the Wilcoxon matched pairs signed ranks test.

The duration of the meal was set as 100% for each subject and the amount of food consumed and the level of satiety at 0%, 25%, 50%, 75% and 100% of the meal was calculated. If these percentages did not coincide temporarily with a satiety rating, the mean between the proceeding and subsequent ratings was used. These calculations allow comparison between eating rate and the rate at which satiety develops. The groups were then compared with one-way ANOVA.

3. Results

A gastrectomized man was excluded from the satiety comparisons. He ate 400 g but said that he never experienced satiety or hunger. His satiety ratings varied between 0.5 and 0.7 during the meal.

The gastrectomized subjects ate somewhat less than controls, but the difference was not statistically significant (Table 1). There was no difference in the duration of the meal or in the level of satiety perceived between gastrectomized and control subjects by the end of the meal (Table 1). The thought of eating was significantly less tempting, and the subjects estimated their hunger as significantly less intense after the meal, and there was no difference between the gastrectomized and the control subjects (Table 1).

The level of CCK-8 before the meal was higher in the gastrectomized subjects than in the control subjects. While control subjects showed an increased level of CCK-8 after the meal, the gastrectomized subjects did not (Table 1).

The rate of eating was somewhat, but not significantly, lower among the gastrectomized subjects than among con-

Table 1
Food intake, meal duration, satiety, thought of eating, feeling of hunger and plasma concentration of cholecystokinin octapeptide (CCK-8) in 10 gastrectomized and eight control subjects

Meal	Gastrectomized		Controls	
	Before	After	Before	After
Food consumed (g)	–	211 \pm 28	–	270 \pm 30
Duration of meal (min)	–	9.2 \pm 1.1	–	10.2 \pm 0.9
Satiety ^a	0	5.3 \pm 0.8 *	0	4.8 \pm 0.7 *
Thought of eating ^{a,b}	8.5 \pm 0.5	4.5 \pm 1.2 *	9.0 \pm 0.8	4.0 \pm 1.0 *
Hunger ^{a,c}	6.0 \pm 1.1	1.0 \pm 0.3 *	7.0 \pm 1.5	1.5 \pm 0.4 *
CCK-8 (pmol/l)	8.7 \pm 0.5 **	8.8 \pm 0.5	5.5 \pm 0.6	8.2 \pm 0.7 *

^a Based on nine gastrectomized subjects.

^b Estimated from very repulsive (0) to very tempting (10).

^c Estimated from not hungry at all (0) to very hungry (10). Values are means \pm S.E.

* $P < .01$ compared to before the meal.

** $P < .01$ compared to controls.

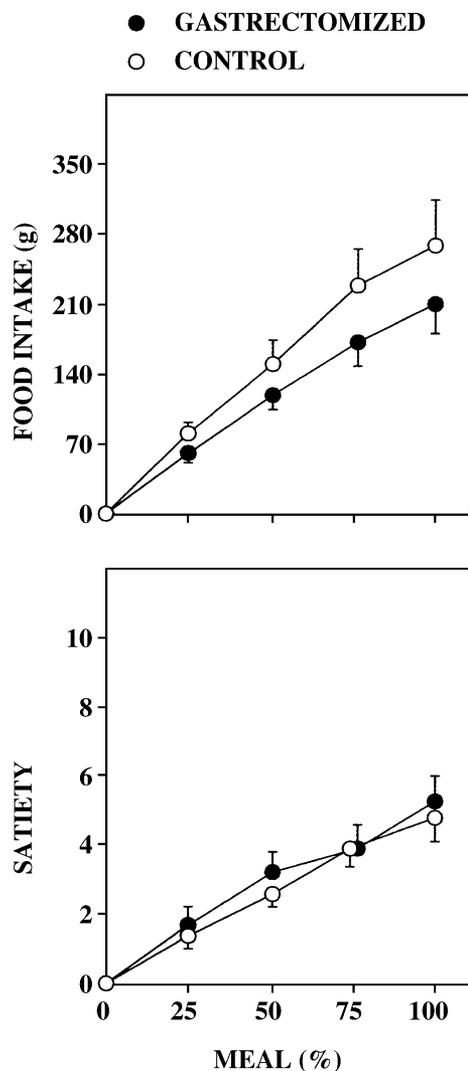


Fig. 1. Food intake and perception of satiety in 10 gastrectomized humans and in eight intact controls. Satiety was rated on a scale from 0 to 10 at 1-min intervals during ongoing eating, and the duration of the meal was set at 100% for each subject. Values are means \pm S.E. The satiety ratings from one gastrectomized subject were excluded.

trols, and the development of satiety was virtually identical (Fig. 1).

4. Discussion

Although there is overwhelming evidence that the stomach is involved in satiety [8,32], postpyloric factors are also likely to contribute both in animals [29] and humans [30]. For example, the effect of gastric distention on hunger and energy intake in humans is relatively short-lived [25], lipid stimulation of the duodenum, jejunum or ileum inhibits food intake [14,37] and surgical bypass of the jejunum and ileum decreases food intake and reduces the desire to eat [22].

The gastrectomized subjects in the present study estimated that eating is as tempting before the meal and as

repulsive after the meal as controls. Similarly, they estimated that their hunger is higher before than after the meal in a manner that was not different from that of controls. In addition, they ate about the same amount of food at the same time and experienced satiety in the same way as intact controls. A gastrectomized man said that he never experienced satiety or hunger, and although he consumed a substantial amount of food, he reported no increase in satiety. We can offer no explanation for the absence of satiety and hunger in this individual, although one wonders why, if he did not feel satiated, he stopped eating, or indeed why he started to eat if he did not feel hungry.

We do not think that the fact the subjects in this study were tested only once undermines the validity of our results. There is little intraindividual variation in human eating behavior tested under conditions which are similar to those used in the present study [38], and all of our subject consumed an amount of food comparable to that of the 40-or-more-year-old men (300 ± 11 g) and women (227 ± 18 g) mentioned in the Methods section. However, it is possible that differences in some other aspect of ingestive behavior, such as intermeal intervals or sensitivity to food deprivation, exist between gastrectomized and intact subjects.

Thus, although the stomach is a part of the substrate for satiety in normal conditions, its function can be replaced. A similar observation on the role of the stomach in hunger was made long ago [36]. However, the patients in our study were examined 8 years after the removal of the stomach, and alterations in food intake, probably as a consequence of malabsorption, have been reported in patients studied earlier after the operation (e.g., [2,3,17,36]). Satiety is normally signalled not only from the stomach but also from the gut [14,37], and regeneration of vagal fibres, damaged during the operation, to sites distal to the pylorus [16] might mediate gut-to-brain information long after gastrectomy.

CCK-8 is a possible physiological satiety peptide [33]. However, satiety was unaccompanied by an increase in blood levels of CCK-8 in the gastrectomized subject, whereas an increase was found in controls. Although the possibility of a localized release of CCK-8 within the gastrointestinal tract in the absence of a parallel release into the circulation cannot be excluded, these results suggest that the role of CCK-8, like that of the stomach, in satiety is redundant. By contrast, CCK receptor antagonist treatment partly reversed the reduction of food intake induced by gastrectomy in rats [41]. However, CCK-peptides were not measured in that study. In the present study, the levels of CCK-8 were higher before the meal in gastrectomized humans than in controls. Interestingly, a similar increase was reported in obese patients 20 years, but not 9 months after jejunoileal bypass surgery [21,22]. Possibly, intestinal feedback mechanisms, which are dependent upon local metabolic events [11], are disrupted after gastrointestinal surgery.

CCK-peptides can affect satiety both by hormonal [23] and paracrine mechanisms [4,9,39] and at several sites

within the gastrointestinal tract [6]. Possibly, therefore, under normal conditions, many potential sites of action are exposed to the CCK that is released peripherally [19]. It seems unlikely that these sites are exposed to elevated levels of CCK in the absence of an increase in peripheral blood [19]. Our findings suggest instead that satiety occurred in the gastrectomized subjects via a CCK-independent mechanism, and therefore, that a normal mechanism of control had been replaced. Such replacement could be exerted by, for example, orosensory feedback, which can compensate for lack of gastric feedback [8]. This may be particularly true in a group of patients such as that studied here, in which the stomach was removed on average 8 years before the behavioral observations, thus allowing ample time for compensatory mechanisms to emerge.

Thus, the present study reemphasizes the possibility that there are probably redundant controls of food intake. The circumstances under which one control mechanism can serve a vicarious function for another, however, have not been explored. This seems an urgent task, as the existence of redundant controls makes it unlikely that the search for simplistic, pharmacologically based tools for weight control, all too common today, will be successful.

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