Satiety signals from the gastrointestinal tract$^{1-3}$

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ABSTRACT Experiments in rats with crossed intestines have shown that signals arising in a 30 cm segment of upper small intestine do not affect the short-term control of food intake. The combined stimulus of neural and hormonal signals arising in the crossed intestinal segment and of absorbed food do not inhibit intake during a subsequent meal. The relevant satiety signals must arise in either the stomach and upper duodenum or in the lower small intestine. A transplanted stomach study has shown that a hormone released from the stomach is responsible for the termination of a single meal. Other studies show that neural or hormonal signals coming from the lower small intestine are important in the regulation of total daily food intake and in the long-term regulation of body weight. Am J Clin Nutr 1985;42:1044–1049.

KEY WORDS Food intake, stomach, intestine, ileum, hormones, CCK, nerves, body weight

Introduction

Several studies have shown that infusion of food into the small intestine produces an immediate reduction in food intake (1–4). Many of these studies have infused food at the unusually rapid rate of 1 ml/min which approximates the rate of feeding in the rat but not the rate of stomach emptying. The main difficulty in interpreting these experiments is deciding whether the food stimulus is sufficiently physiological to cause a normal feeling of satiety. Feeding behavior can be affected by many nonphysiological stimuli that cause the animal to feel uncomfortable or to experience malaise.

Studies in rats with crossed intestines

One method of delivering ingested food to the small intestine in a physiological way is through the use of the crossed-intestine preparation (5, 6). In this preparation, a pair of parabiotic rats undergo an operation in which a 30 cm segment of the lower duodenum and upper jejunum of each rat in a pair is disconnected from its own intestine and reconnected to the intestine of its partner. Food eaten by one of the rats leaves its own stomach, travels through the upper duodenum and then passes into the intestine of its partner. After moving through the 30 cm crossed segment of the partner’s upper small intestine, the remaining unabsorbed food returns to the intestine of the rat that fed. The preparation is symmetrical so that each rat feeds both itself and its partner.

This method of delivering food to the small intestine of the partner rat is highly physiological. The food eaten by one rat is mixed with saliva during feeding, swallowed, and then processed by gastric secretions in its stomach. It is released from the stomach at a near physiological rate and then mixed with pancreatic and intestinal secretions just before it passes into the intestine of the other rat. The food stimulus that arrives in the partner rat’s intestine is as physiological as if the partner had eaten the food itself.

This surgical preparation can be used to determine whether physiological signals arising in the 30 cm crossed intestinal segment are involved in the termination of a meal. If one rat of each pair is fed alone, then this rat will lack signals arising in its own crossed segment because this segment is connected to the other rat’s intestine. If signals arising in this segment

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normally inhibit food intake, then this rat should overeat. In contrast, the other rat that is allowed to eat 30 or 60 min later should consume less because the ingested food will already have been present in its crossed-intestinal segment. Contrary to our expectation, we found that crossing the intestines of these parabiotic rats had no effect on their short-term food intake. These rats ate the same amount of food under the same conditions as control parabiotic rats that did not have their intestines crossed.

This result would be expected if food failed to arrive in the crossed segment of the intestine by the time that the second rat was fed. To check that food had in fact arrived, we added a small amount of radioactive glucose or amino acid to the standard liquid diet that one of the rats was allowed to eat. Every 10 min after the meal began, a small sample of blood was withdrawn from the tail of both rats and analyzed for radioactive content. We found that after only one rat had fed, about equal amounts of radioactive label were present in the blood stream of both rats with crossed intestines. Food had been absorbed into both rats within a few minutes after the food arrived in the stomach of the fed rat and the absorbed glucose and amino acids were present in about equal amounts in both rats when the second rat was fed at 30 or 60 min (5). Thus, food was absorbed from the crossed intestinal segment but it had no effect on subsequent food intake.

We conclude from this study that signals arising in the 30 cm crossed segment of the upper small intestine do not alter food intake. These signals include neural messages about the presence of glucose or amino acids in the lumen of the crossed intestinal segment (7–9) and hormones such as CCK, GIP, and motilin that are released from this segment (10). The role of CCK in the termination of food intake was specifically investigated in rats with crossed intestines by measuring pancreatic enzyme flow, the bioassay for the presence of CCK in the blood stream. As in previous studies, we fed one of the rats with crossed intestines first. We found that the rat that was fed and was fully satiated had a nonsignificant increase in enzyme flow while the crossed-intestine partner that remained hungry had a large increase in flow that was comparable to that of the fed and sated control rat (11). Apparently, CCK was released by the 30 cm crossed segment and was present at normal postmeal levels in the bloodstream of the hungry rat but was not present in the blood of the satiated rat. In short, the presence of CCK in the bloodstream did not inhibit food intake in the hungry rat and was not necessary for the fed rat to feel satiated. High plasma levels of CCK were completely dissociated from the state of satiety in the rat.

The final and most important signal that was eliminated by the crossed-intestine experiment was absorbed food. The nutrients absorbed from the crossed segment had no effect at all on subsequent food intake. Since absorbed food travels through the portal vein directly to the liver, it seems unlikely that this organ is involved in the short-term inhibition of intake (12). Instead, the signal must arise in the stomach and upper duodenum or in the lower small intestine. A number of experiments show that there is a short-term satiety signal that comes from the stomach (6, 13). These studies are consistent with the work of Davis and Campbell (14) and of Deutsch and colleagues (15, 16); however, they go one step further. They show that the signal arising in the stomach is a hormone and this hormone is released by the combined stimulus of gastric distension and chemical stimulation of the stomach wall (13).

The seeming contradiction between our studies in rats with crossed intestine and several other infusion studies published in the literature (1–4) led us to investigate further the infusion of food directly into the small intestine. A graduate student, Resit Canbayli, and I chose to infuse a balanced diet, Nutrament (Mead-Johnson Nutritional, Evansville, Indiana, 1 kcal/ml), into the upper portion of the crossed intestinal segment at a very slow rate. Although we realized that the infused food would not be in its physiological form when it arrived in the jejunum, we chose a rate, 3.6 ml/h or 0.06 ml/min, which would deliver a physiological amount of food to the rat's intestine in 24 h, ie 85–90 kcal. The liquid diet was delivered to the upper jejunum of the crossed segment about 7–8 cm from the first cross-over point and about 2–3 cm below the ligament of Trietz. We found that the infusion led to a nonsignificant reduction in intake of
the first meal, a reduction in the total daily food intake of the pair of rats. This reduction nearly compensated for the amount of food infused. Although both rats showed a measurable reduction of total daily food intake, the reduction in intake was only significant for the rat that did not have the food infused directly into its crossed-intestinal segment. Apparently, the infused food moved down into the partner’s lower jejunum and ileum and significantly inhibited this rat’s total daily food intake from this site. This result suggests that the lower small intestine might play a long-term role in the inhibition of food intake.

Signals from the lower gut

The importance of the lower small intestine for the long-term control of food intake and body weight had previous support from studies on the effectiveness of the jejunoileal bypass in the treatment of morbid obesity in man (17–20). In jejunoileal bypass surgery, the upper part of the jejunum is connected to the lower ileum leaving a long segment of nonfunctional bowel. The rationale behind the original use of this surgery was to prevent the absorption of food in the small intestine so that obese patients could eat as much as they pleased but the unabsorbed food would simply pass out the other end. An incidental side effect of the operation was that the lower small intestine and the colon were stimulated to a much greater extent than usual by unabsorbed food.

Several years after it had been shown that the jejunoileal bypass was effective in causing a substantial reduction in body weight, it was discovered that the main result of the operation in man was the reduction of food intake during the postoperative period (21, 22). Sclafani and I have confirmed this finding in obese rats (23). We found that the observed reduction in food intake of our rats almost completely explained the measured loss in body weight. We thought that the reduction of intake might be due to the stimulation of the lower gut with unabsorbed food rather than to the immediate discomfort induced by the operation or to the long-term malaise caused by malabsorption in patients and rats. To test this hypothesis, we devised a new operation that would cause an unusual stimulation of the lower small intestine but would not cause discomfort through malabsorption or through the release of toxic substances by the bacteria in the bypassed intestinal segment. In this operation, a 10 or 20 cm segment of the ileum was transposed to the middle of the duodenum (24–26). Food eaten by the rat moved from its stomach through the upper duodenum into the transposed ileal segment. After moving through the ileal segment, the unabsorbed food returned to the lower duodenum and continued down the remaining reconstructed small intestine. This operation differs from the jejunoileal bypass in that it does not alter the length of the functional small intestine and there is no bypassed segment. Thus, malabsorption or toxic factors arising in the bypassed segment could not be responsible for causing a reduction in food intake. We found that this operation was as effective in causing weight loss in obese rats as was the jejunoileal bypass (27). The results of this operation suggested that stimulation of the ileum by nutrient-rich chyme could cause a reduction of food intake until a new level of body weight was reached. In another experiment, we measured the postprandial levels of various gut peptides in rats with either ileal transposition or jejunoileal bypass (26). We found that the plasma level of the lower gut hormone, enteroglucagon, was greatly elevated while the levels of the upper gut hormones, gastrin, GIP, and insulin, were significantly lower in the experimental animals as compared to controls.

In short, a signal resulting from stimulation of the lower gut with undigested food is able to cause a sustained reduction of food intake. Although we had eliminated many of the malaise-inducing medical problems associated with the jejunoileal bypass operation, we were worried that increased levels of lower gut hormones might cause the animals some discomfort. In fact, I have been able to show in a recent experiment (28) that both the jejunoileal bypass and the ileal transposition operation produce a conditioned aversion to a novel flavor introduced into the rat’s drinking water immediately after surgery. This result is a warning sign that the reduction of food intake may be caused by malaise.

To explore further the role of the lower gastrointestinal tract in the control of food intake, it is important to find a way to reduce the number of signals arising in the lower gut and
see whether this produces an increase in feeding behavior. An increase in food intake is more difficult to interpret as having been caused by discomfort. To do this, we used a new operation in parabiotic rats. The intestine of one rat of the pair was transected 20 cm above the cecum. The upper end was sewn end-to-side to the other rat's intestine 20 cm above its ileocecal valve. The lower end was simply closed so that no further undigested food could enter into the lower intestine of this rat. The partner's lower gut beginning 20 cm above the cecum was stimulated by the undigested food eaten by both rats.

We measured the feeding behavior of both rats in five pairs of animals and found that soon after surgery the rat that had its lower gut doubly stimulated by undigested food reduced its food intake and kept its intake below presurgical levels (25). The other rats that had their lower gut unstimulated slowly increased their food intake over 3 wk. During the last week, they ate significantly more than they had in the presurgical baseline period. This result suggested that the lower gut might play a role in the long-term control of total daily food intake. It was important to check, however, that the observed changes in food intake were not caused simply by the loss of calories from the lower intestine of one rat to its partner. At the end of 3 wk, 4 pairs of rats were killed. It was found that the rats that ate more food weighed 499 ± 53 g which was significantly more than their partners that weighed 414 ± 40 g (p < 0.05). There was also a nearly significant increase in dissectable abdominal fat. Thus, the rats both overate and became relatively obese. The observed changes in food intake could be explained by two approximately equal factors: a loss of food from one rat to the other and an increase in food intake that made the rat with the unstimulated lower gut both heavier and fatter than its partner. Apparently, signals arising in the lower gut play some role in controlling long-term food intake and body weight.

These studies on the role of the lower small intestine in the control of food intake have received support from recent research on diabetics. Various clinical experiments aimed at lowering the blood sugar level of diabetic patients have used digestive enzyme inhibitors, dietary fiber or poorly-digested food to reduce the rate at which food is digested and absorbed (29–31). The obvious consequence of these manipulations is that more unabsorbed food will be present in the lower part of the digestive tract. Studies using the amylase inhibitor, acarbose, have shown a dose related inhibition of food intake and a significant loss of body weight at the higher doses in rats and diabetic man (32–35). Although the cause of the reduction of food intake is not clearly understood, the probable cause is the greater presence of undigested and unabsorbed food in the lower small intestine and colon. These nutrients should stimulate the mucosa of the lower gut while being absorbed and provoke the release of neural or hormonal signals that inhibit food intake. The importance of lower gut stimulation in the control of food intake is also consistent with epidemiological data that show that those countries that have a high fiber content in their standard diet are much less prone to obesity and obesity-related diseases (36–38). Recent work on various foods that reduce postprandial plasma glucose levels in type II diabetics suggest that the critical factor may not be the fiber content of the diet but the presence of various foods in the diet that are poorly and slowly absorbed, such as beans and peas (31, 39). The main result of the presence of fiber or the less digestible foods in the diet is to move ingested food further down the digestive tract before it is absorbed. This unabsorbed food in the ileum and colon stimulates lower gut mucosa to release signals that inhibit food intake. Thus, the reduced food intake after acarbose and the reduced obesity in populations that subsist on high fiber and slowly-digested foods may be caused by an increase in satiety signals from the lower gut.

Conclusion

Studies in rats with crossed intestines have shown that signals arising in the lower duodenum and upper jejunum have no effect on the short-term control of food intake. These signals include neural and hormonal messages arising in the crossed-intestinal segment as well as absorbed food. Since the absorbed food travels directly to the liver and causes changes in metabolism in both the liver and adipose tissue, these organs also do not seem to be in-
involved in the short-term control of food intake. Instead, the signal that inhibits short-term feeding must arise in the stomach and upper duodenum or in the lower small intestine. One of my studies has shown that a hormonal signal arising in the stomach causes a reduction in short-term food intake. This hormone is released by the combined stimulus of stomach distension and chemical stimulation of the gastric mucosa. Two other types of studies have shown that signals arising in the lower gut also cause changes in food intake that occur over several days and that lead to long-term changes in body weight and body fat. In two studies that involved the transposition of a short 10 or 20 cm segment of lower ileum to the upper small intestine, the rats showed a reduction of food intake and body weight that depended upon the length of the transposed ileal segment. In another study in which the lower ileum and the colon were either doubly stimulated or unstimulated with food, there were large and persistent changes of food intake that were consistent with the lower gut theory. These studies are supported by recent work on enzyme inhibitors and on certain slowly-digested foods that draw undigested food down into the lower gut and effectively inhibit food intake. Apparently, the lower gut plays a role in the long-term regulation of food intake and body weight.

References

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