Gastric Pacing for Morbid Obesity: Plasma Levels of Gastrointestinal Peptides and Leptin

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Abstract

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Objective: A gastric pacemaker has been developed to treat morbid obesity. Patients experience increased satiety, the ability to reduce food intake, and a resultant weight loss. However, the mechanism behind the changed eating behavior in paced patients is still under investigation.

Research Methods and Procedures: This study was performed on 11 morbidly obese patients (mean BMI, 46.0 kg/m^2) treated with gastric pacing. The peripheral blood levels of satiety signals of cholecystokinin (CCK), somatostatin, glucagon-like peptide-1 (GLP-1), and leptin were studied 1 month before gastric pacer implantation, 1 month after implantation, and 6 months after activation of electrical stimulation. Blood samples were drawn 12 hours after fasting and in response to a hypocaloric meal (270 kcal). Patients were followed monthly for vital signs and weight level.

Results: Gastric pacing resulted in a significant weight loss of a mean of 10.4 kg (4.4 BMI units). No negative side effects or complications were observed during the treatment. After activation of the pacemaker, meal-related response of CCK and somatostatin and basal levels of GLP-1 and leptin were significantly reduced ($p < 0.05$) compared with the tests before gastric pacing. The weight loss correlated significantly with a decrease of leptin levels ($R = 0.79$, $p < 0.01$).

Discussion: Gastric pacing is a novel and promising therapy for morbid obesity. Activation of the gastric pacer was associated with a decrease in plasma levels of CCK, somatostatin, GLP-1, and leptin. More studies are necessary to elucidate the correlations between satiety, weight loss, and digestive neuro-hormone changes.

Key words: morbid obesity, gastric pacing, gastrointestinal peptides, appetite, leptin

Introduction

An implantable gastric stimulator system has been designed to provide electrical stimulation of the stomach for the control of gastric electromotor activity and food intake. The effect of long-term gastric pacing on food intake and body weight was first studied in pigs (1,2). Gastric pacing in the animals caused changed eating behavior and weight loss. The experiments showed a reduction in the total amount of food eaten per day because of a reduction of number of meals. Weight change displayed a cyclic pattern (2 weeks of weight gain followed by 1 week of weight loss), resulting in a net weight loss. The cyclic shape of weight change and the abnormal modality of food intake were similar to what have been observed after posterior hemivagotomy in experiments in rats and rabbits (3,4). These results suggest that gastric pacing causes a change in parasympathetic activity.

Because gastric pacing showed promising results in pigs, the technique was further refined for treatment of obesity in humans. The intention was to obtain a technique that induces weight loss with minimal interference of normal physiology and has as few side effects as possible. Evaluation of gastric pacing in 24 morbidly obese humans has been recently published (5). It concluded that gastric pacing resulted in a significant weight loss (mean of 4.7 BMI units/9 months) without any medical problems and few technical incidents. The patients reported increased satiety, leading to reduce food intake. It was suggested that gastric pacing facilitates weight loss by enhancing neuroendocrine satiety mechanisms. The safety and efficacy of this form of therapy is being evaluated in clinical trials in many countries. Preliminary data from these studies have been published (6–8).

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Cholecystokinin (CCK),[1] somatostatin, and glucagon-like peptide-1 (GLP-1) are vagally regulated gastrointestinal peptides important for satiety (9). CCK is released from the small intestine in response to a meal and exerts well-known gastrointestinal effects such as stimulation of gallbladder contraction, stimulation of pancreatic exocrine secretion, and inhibition of gastric emptying (10). Furthermore, it is known that exogenously administered CCK reduces food intake (11). The mechanism for the satiety action of CCK seems to involve activation of CCK-A receptors on abdominal vagal afferents signaling satiety to the brain (12). Somatostatin inhibits gastrointestinal motility and exocrine and endocrine secretions and has also been demonstrated to decrease food intake (13). GLP-1 is secreted from the lower gut in response to food intake, and it stimulates insulin secretion and inhibits gastric emptying (14). Studies in humans have shown that peripheral administration of GLP-1 decreases food intake (15).

Leptin, the protein hormone encoded by the *ob* gene, is secreted primarily from adipose tissue and plays an important role in the regulation of food intake (16). This hormone acts on the hypothalamus to reduce food intake and increase energy expenditure. However, resistance to the proposed antiobesity action of leptin has been described, as reflected by increased levels of leptin in obese subjects in relation to an increased amount of body fat (17).

The aim of this study was to study possible mechanisms of increased satiety in obese humans treated with gastric pacing. We analyzed basal and meal-related plasma levels of CCK, somatostatin, GLP-1, and leptin in relation to gastric pacing and body weight changes in morbidly obese humans.

Research Methods and Procedures

Subjects

Eleven obese patients (nine women and two men) were recruited from the Health District of Venice at "Umberto 1st" Hospital in Venice and University of Verona, Italy. The weight inclusion criterion was BMI >40 kg/m^2. All patients had previously received instruction on diet and lifestyle modifications and were unsuccessful in achieving and maintaining weight loss. Besides obesity, the patients had no other disease, and they had no history of previous gastrointestinal surgery. None of the patients were taking medication or had been taking oral contraceptives at least 2 months preceding the investigation. Smokers were excluded. The research protocol was approved by the Ethics Committee of Venice, Italy, and informed consent was obtained from each patient.

[1] Nonstandard abbreviations: CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; IGS, electrical stimulator system; RIA, radioimmunoassay; AUC, area under the curve.

Surgical Procedure and Gastric Pacing

The electrical stimulator system (IGS) is composed of a bipolar electro-catheter (the gastric lead), tunnelized in the gastric wall, and a gastric pacemaker or gastric pacer (battery with a microcircuit) connected to the lead and located outside the abdomen (Figure 1). The IGS was implanted by laparoscopic or open surgery under general anesthesia. The lead was tunnelized intramuscularly at the lesser curve of the anterior gastric wall (upper third of antrum). Intraoperative fiber optic flexible endogastroscopy was performed to ensure that the mucosa was undamaged during electrode implantation and no intracavity penetration had occurred. After placement of the lead, the gastric pacer was located in a subcutaneous pocket created in the anterior abdominal wall. Gastric pacers and leads were supplied by Transneuronix Inc. (Mt. Arlington, NJ). The IGS was interrogated using transcutaneous radiofrequency telemetry, which linked the implanted device to a computerized programmer. Telemetric data included programmed electrical stimulation parameters, the impedance of the circuit, and residual battery charge.

Postoperatively, patients were not prescribed any specific diet but encouraged to eat three main meals per day or less and to avoid snacks between meals. Ingestion of high caloric beverages and alcohol was discouraged.

Experimental Design

Weight and vital signs were measured before implant and monthly after implant. Standardized meal tests were performed $\sim$1 month before implantation, 1 month after implantation just before the activation was started, and after $\sim$6 months of electrical stimulation. The experiments started in the morning after 12 hours of overnight fasting. An indwelling catheter was inserted into a forearm vein to collect five blood samples (10 mL each) during the 5-hour course of the experiment. The first blood sample was drawn at 8 AM in a fasting state, and then the patients were fed a standardized hypocaloric meal consisting of 270 kcal composed of 12% proteins, 39% lipids, and 49% carbohydrates. Additional blood samples were drawn 30, 60, 120, and 300 minutes after the start of eating. Blood samples were collected in chilled tubes containing aprotinin (500 IU/mL) and EDTA (1 mg/mL). Samples were centrifuged for 10 minutes at 1500*g* and 0 °C, and plasma was removed and stored at -80 °C in 0.5-mL aliquots until analyzed.

Analytical Methods

Plasma concentrations of CCK were determined by radioimmunoassay (RIA), using a commercial kit (EuroDiagnostica AB, Malmö, Sweden). Before the RIA, 1 mL of plasma was extracted using SEP-PAK C18 microcolumns (Water Associates, Milford, MA) (18). CCK was eluted with 5 mL of a mixture of acetonitrile and 0.1% acetic acid in equal proportions. The eluate was evaporated

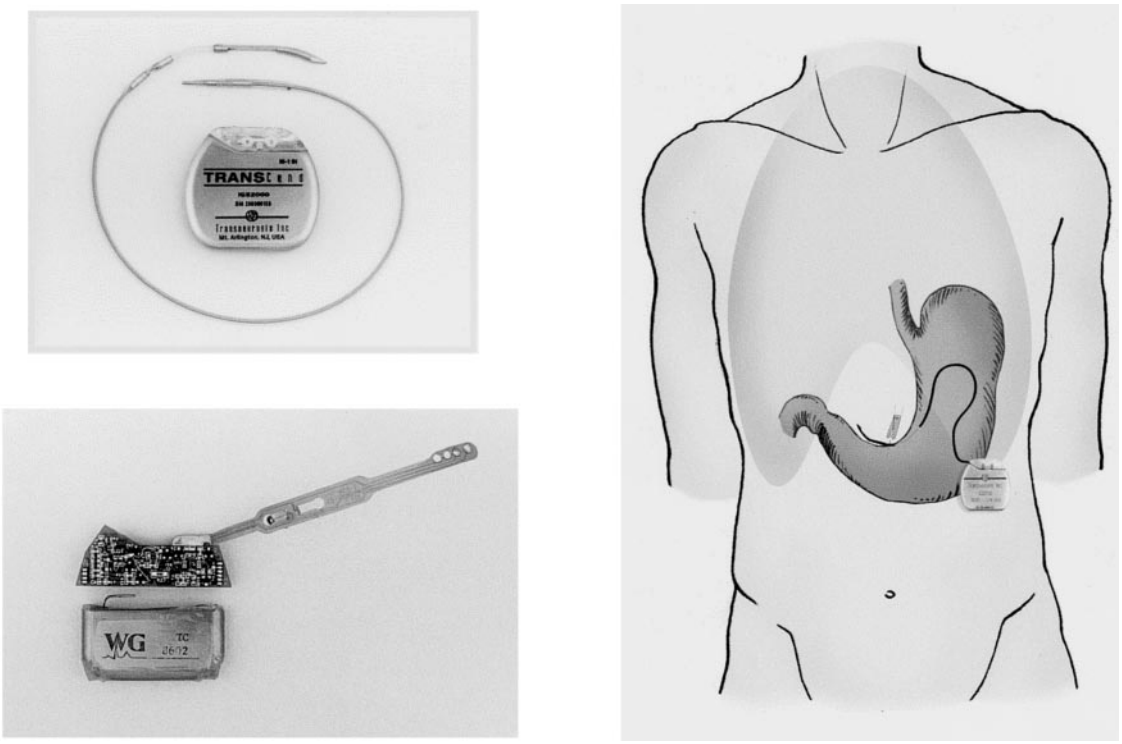

Figure 1: The IGS is composed of a bipolar electro-catheter and a gastric pacemaker or gastric pacer. A battery and a microcircuit compose the gastric pacer (size: 50 × 48 × 10 mm^3; weight: 40 g; longevity: 4 to 5 years).

to dryness in vacuo. The dry extract was reconstituted in phosphate buffer and analyzed for CCK according to the protocol specified by the manufacturer. The detection limit of the assay was 0.5 pM; the intra-assay variation was 5.5% within the range of concentrations measured, and interassay variation was 13.7%.

Somatostatin levels were measured with a RIA kit (EuroDiagnostica AB) after extraction of the plasma samples. The extraction procedure was based on the use of SEP-PAK C18 microcolumns. One milliliter of plasma was applied on the column, and somatostatin was eluted with 2 mL of methanol. The eluate was evaporated to dryness and dissolved in the assay diluent for determination of somatostatin according to the manufacturers′ protocol. The rabbit antiserum binds to the common cyclic part of both somatostatin-14 and -28. Detection limit and intra- and interassay variations were 6 pM, 8.3%, and 6.4%, respectively.

Plasma levels of bioactive GLP-1 were measured using a commercial ELISA kit (LINCO Research, Inc., Falkenberg, Sweden). Detection limit and intra- and interassay variations were 2 pM, 7.0%, and 9.8%, respectively.

Leptin levels were determined by a human leptin RIA kit (LINCO Research, Inc.). Detection limit and intra- and interassay variations were 0.5 ng/mL, 5.0%, and 4.5%, respectively.

Calculations and Statistics

Values are expressed as mean ± SE. Excess BMI (amount of BMI > 25 kg/m^2) was calculated. Weight loss is expressed as percent excess BMI loss [(BMI initial − BMI actual)/(BMI initial − 25) × 100]. Meal-related response of CCK and somatostatin were summarized by the area under the curve (AUC) for values measured 0 to 300 minutes after food intake. A one-way repeated measures ANOVA was used to analyze the AUC data. The within factor was visit with three levels (visit 1 = before implantation, visit 2 = after implantation, visit 3 = pace activation). A specific hypothesis about the first two visits vs. the last visit is referred to as a priori contrast and was performed despite an insignificant *F*-test.

For GLP-1 and leptin data, AUC was not used because the levels were unchanged in response to food intake. They were analyzed by a two-way ANOVA with repeated measures on two factors. The factors were visits and minutes after food intake (0, 30, 60, 120, and 300 minutes). The distribution for the GLP-1 variable is skewed. The data have been log-transformed to meet requirements for an adequate ANOVA. Baseline data (0 minutes) for all hormones were analyzed by one-way repeated measures ANOVA with visit as the factor. Spearman rank correlation was calculated to evaluate the association between variables.

Table 1. Anthropometric parameters in the patients studied

	Patients
Number	11
Gender (f/m)	9/2
Age (years)	39.4 ± 3.4
Weight (kg)	121.7 ± 5.1
BMI (kg/m^2)	46.0 ± 2.5

Values are mean ± SE.

Results

Table 1 shows age and anthropometric data of the patients. Figure 2 shows weight loss expressed as percent excess BMI loss during 6 months after implantation of the pacemaker. Weight loss, BMI loss, and percent excess BMI loss of the patients at visits 2 and 3 are presented in Table 2. Weight and BMI were significantly reduced at visit 3 compared with visit 1 ($p < 0.01$).

No clinical complications occurred during the course of the study, and there were no failures of the gastric stimulator system or the lead. Surgically, there was one reoperation for bleeding and one to revise the generator pocket.

Basal levels of CCK were not significantly changed at the different visits. However, the integrated CCK response to the test meal (AUC) was significantly reduced after activation of the pacemaker compared with the responses at the first two visits ($p < 0.05$; Figure 3). Basal levels of somatostatin were significantly lower after activation of the pacemaker compared with the first two visits ($p < 0.05$). The meal-related somatostatin response (AUC) was also significantly decreased at visit 3 compared with visits 1 and 2 ($p < 0.05$; Figure 4).

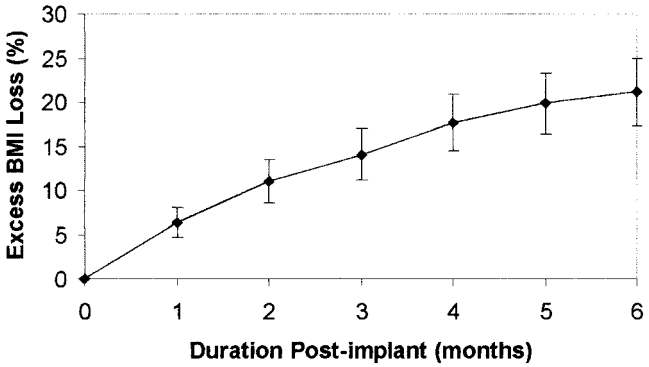

Figure 2: Weight loss of the patients expressed as mean ± SE percentage excess BMI loss during 6 months after implantation of the pacemaker. Weight was significantly reduced after 6 months of treatment with the gastric pacer ($p < 0.01$).

Table 2. Weight loss, BMI loss, and percent excess BMI loss of the patients

	Visit 2 (after implantation)	Visit 3 (after pacer activation)
Weight loss (kg)	3.6 ± 0.7	10.4 ± 2.7
BMI loss	1.3 ± 0.3	4.4 ± 1.2
Percent excess BMI loss	7.0 ± 1.7	20.2 ± 3.8

Values are mean ± SE.
Percent excess BMI loss = (BMI initial − BMI actual)/(BMI initial − 25) × 100.

Basal levels of GLP-1 were significantly reduced after activation of the pacemaker than before and after implantation ($p < 0.05$). GLP-1 levels were not significantly changed in response to food intake, whereas repeated measure curves of GLP-1 levels were significantly decreased at visit 3 compared with visits 1 and 2 ($p < 0.01$ and $p < 0.05$, respectively; Figure 5). Basal levels of leptin were significantly lower at both visits 2 and 3 compared with visit 1 ($p < 0.01$ and $p < 0.05$, respectively; Figure 6). However, there was no change of leptin levels in response to the meal test.

Weight loss (visit 1 to visit 3) correlated significantly with decrease of leptin levels ($R = 0.79$, $p < 0.01$).

Discussion

In this study, we have investigated certain satiety signals as possible mechanisms for changed eating behavior and

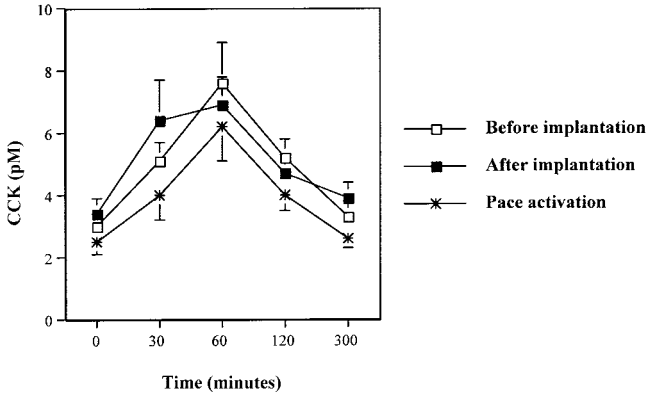

Figure 3: Plasma CCK levels in response to a test meal in the patients before implantation, after implantation, and after activation of the gastric pacemaker. The meal begins at 0 minutes. Values are mean ± SE. The integrated postprandial response (AUC) was significantly lower after activation of the pacemaker than before and after implantation ($p < 0.05$).

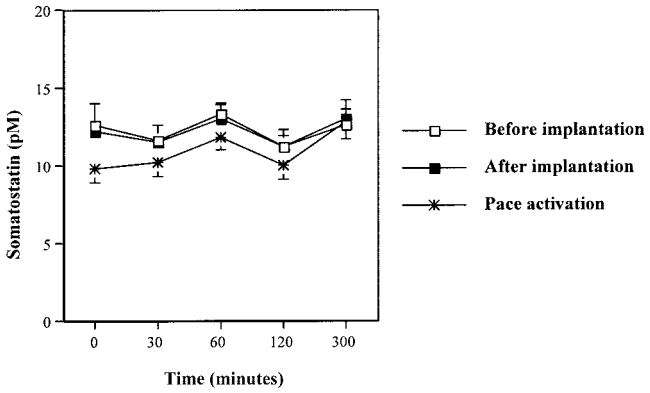

Figure 4: Plasma somatostatin levels in response to a test meal in the patients before implantation, after implantation, and after activation of the gastric pacemaker. The meal begins at 0 minutes. Values are mean ± SE. Basal levels and the integrated postprandial responses (AUC) were significantly lower after activation of the pacemaker than before and after implantation ($p < 0.05$).

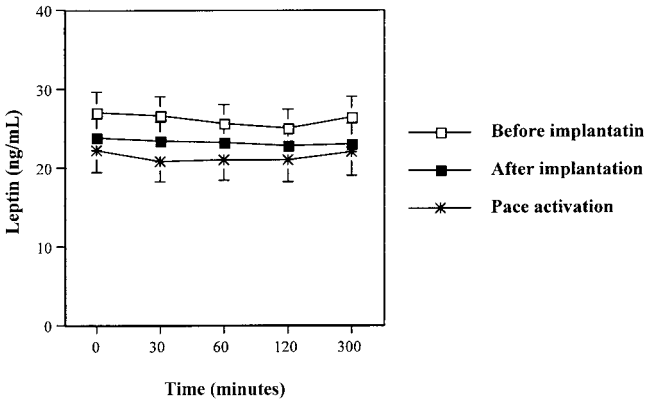

Figure 6: Plasma leptin levels in response to a test meal in the patients before implantation, after implantation, and after activation of the gastric pacemaker. The meal begins at 0 minutes. Values are mean ± SE. Basal levels and repeated measures were significantly lower at visit 2 compared with visit 1 ($p < 0.01$ and $p < 0.05$, respectively), and basal levels were significantly decreased at visit 3 compared with visit 1 ($p < 0.05$).

weight loss in obese subjects treated with gastric pacing. Six months of treatment resulted in significant weight loss and reduced plasma levels of CCK, somatostatin, GLP-1, and leptin levels associated with activation of the gastric pacemaker. The decrease in leptin levels correlated with weight loss.

CCK is considered a physiological meal-related satiety signal, and peripheral levels of CCK have been shown to correlate with subjective satiety (18). Thus, patients with bulimia nervosa have impairment in postprandial release of CCK and less satiety than controls (19), whereas anorectic patients have increased release of CCK (20). Somatostatin and GLP-1 have been suggested to play a physiological role as regulators of intermeal satiety (13,15). It was therefore unexpected to find decreased levels of these gastrointestinal peptides in relation to pace activation. Previously, it has been reported that obese subjects have a lower GLP-1 release after a meal, which may imply a shorter intermeal satiety compared with lean subjects (21). In this study, we found no significant meal-related response of GLP-1. Peripheral levels of leptin are known to correlate with the amount of adipose tissue but do not respond to food intake in humans (9,17). The reduced levels of leptin in this study probably reflect the reduced amount of body fat rather than change of satiety.

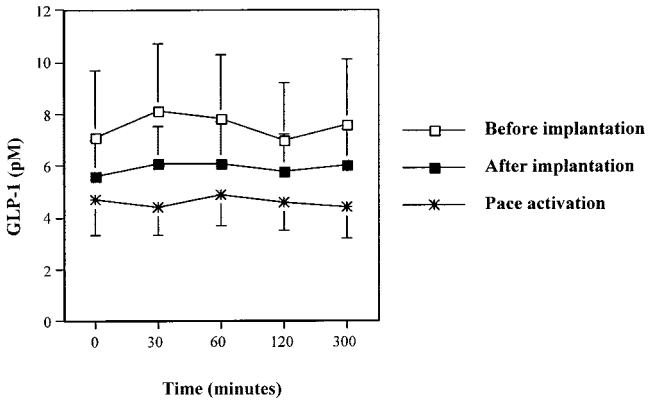

Figure 5: Plasma GLP-1 levels in response to a test meal in the patients before implantation, after implantation, and after activation of the gastric pacemaker. The meal begins at 0 minutes. Values are mean ± SE. Repeated measure curves were significantly lower after activation of the pacemaker than before and after implantation ($p < 0.01$ and $p < 0.05$, respectively).

CCK, somatostatin, GLP-1, and leptin are all under vagal control. CCK is released into the circulation in response to electrical vagal stimulation (22). It may be released from the small intestine but also from vagal nerve terminals because CCK is stored in the vagus nerve (22). Vagotomy abolishes the release of CCK (23). Plasma somatostatin levels are primarily dependent on intact vagal pathways. Vagal blockade, as well as vagotomy, decreases basal and postprandial somatostatin levels, whereas restoration of vagal function increases somatostatin levels (24,25). GLP-1 is released in response to electrical vagal nerve stimulation, and vagotomy abolishes fat-induced release of this peptide (26). Leptin mRNA and leptin protein have been detected in human gastric mucosa (27), and it has been demonstrated that vagal nerve stimulation increases leptin secretion in the human stomach (28). However, peripheral levels of leptin may not reflect luminal secretion of the hormone. Although gastric pacing does not directly stimulate the vagus nerve, there are preliminary indications of changed parasympathetic activity during pace activation (i.e., increased gastric mucous pro-

duction). The decreased levels of gastrointestinal hormones might be more compatible with a depressed vagal tone rather than with an electrical vagal stimulation of the pes ancerinus area (the vagal branches spreading zone in the lesser curve of the stomach). However, it is also possible that gastric pacing leads to parasympathetic hyperstimulation and depletion of stored peptides, which may explain the reduced plasma levels of CCK, somatostatin, and GLP-1.

The mechanism whereby gastric pacing induces changed eating behavior in obesity and weight loss is still under investigation. During treatment, patients report increased meal-related satiety as well as enhanced intermeal satiety. It is not excluded that gastrointestinal satiety signals may be involved in the mechanism, although we found reduced levels of CCK, somatostatin, and GLP-1. Hypothetically, increased receptor sensitivity may be developed as an adaptation to depletion of stored peptides or there may be other satiety signals involved, which have not been investigated in this study. The role of leptin as a satiety signal in humans is not elucidated. Several clinical trials have failed to attain weight loss by leptin treatment. However, recently it was demonstrated that exogenous leptin caused additional weight loss during severe energy restriction (29), suggesting that falling concentrations of leptin during starvation increases appetite in humans. As shown in previous studies (10,30), reduced leptin levels correlated with weight loss. However, this may not be related to appetite but rather to a reduced amount of body fat.

Another possible mechanism of gastric pacing is the influence on gastrointestinal motility. Changed gastrointestinal motility may affect satiety and absorption of nourishment. Unfortunately, little is known about how gastric pacing affects gastric function. Studies on gastrointestinal motility during gastric pacing are under investigation in obese patients. In a recent publication, it was demonstrated that short-term gastric electrical stimulation in dogs reduced food intake and weight without any significant change in gastric emptying (31). At present, we cannot tell whether decreased release of gastrointestinal peptides during gastric pacing in obese patients is a consequence of altered neural input or secondary to changed gastrointestinal motor activity. More studies are needed to elucidate these mechanisms.

Gastric pacing is a novel approach to treat obesity: less aggressive than the usual surgical procedures and with no side effects compared with long-term drug therapy or bariatric surgery. We investigated some satiety signals as possible mechanisms for the weight-reducing effect and found decreased plasma levels of CCK, somatostatin, GLP-1, and leptin associated with activation of the gastric pacer. Weight loss correlated with a decrease of leptin levels, probably because of a decreased amount of body fat. Further studies are needed to elucidate associations between gastrointestinal hormones, satiety, and weight loss during treatment with gastric pacing.

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