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Ghrelin Does Not Predict Adaptive Hyperphagia in Patients With Short Bowel Syndrome

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Abstract

Background—Adaptive hyperphagia is associated with reduced dependence on parenteral nutrition in patients with short bowel syndrome, but mechanisms have not been described. Ghrelin (GHR) has orexigenic effects, whereas peptide YY (PYY) reduces intake. GHR also acts as a hormone to control body fat stores. The authors evaluated whether GHR or PYY was related to caloric intake or absorption in patients with short bowel syndrome and whether GHR was associated with body mass index.

Methods—Patients were admitted twice for nutrient balance. Height and body weight were obtained using standardized protocols. Energy intake >40 kcal/kg/day was defined as adaptive hyperphagia. Fasting plasma PYY and GHR were assayed in duplicate with Linco enzyme-linked immunosorbent assay kits.

Results—The median age of the 7 study participants was 62 (range, 45–66) years, time with short bowel syndrome was 6.6 (range, 2–29) years, and body mass index was 21.2 kg/m^2 (range, 19–27.7). Five patients had adaptive hyperphagia. Neither GHR nor PYY was significantly related to energy intake or absorption (GHR: $R = 0.22$ and $R = -0.233$, PYY: $R = 0.10$ and $R = -0.13$). Body mass index trended toward an inverse association with GHR (GHR: $R = -0.540$, $P = .211$).

Conclusion—The rigorous adaptive hyperphagia seen in these patients with short bowel syndrome was not related to fasting GHR or PYY, suggesting the need to explore other mechanisms.

Keywords

short bowel syndrome; intestinal hormones; ghrelin; peptide YY

Background

Short bowel syndrome (SBS) is a condition where massive sections of small and often large intestine are lost due to thrombosis of the superior mesenteric artery or vein in response to clotting disorders, torsion of the bowel on its mesentery, volvulus, or blunt abdominal trauma.[1] Alternatively, resection of segments of small intestine damaged by inflammatory bowel disease or abdominal radiation may leave the patient with <180 cm small intestine

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with such severe nutrient malabsorption that parenteral nutrition (PN) is needed to maintain nutrition status and health.[1]

A process of intestinal adaptation occurs whereby the remaining small intestine hypertrophies and dilates, increasing the absorptive surface area. This develops over a period of 1–2 years after the initial SBS surgery, in response to oral food intake.[1–3]

A distinct process termed *adaptive hyperphagia* (AH) has been described wherein the intake of dietary energy is greatly increased after the initial period of adaptation.[4] In 90 patients with SBS, of whom 62% had colon in continuity, oral intake and fecal output were measured to describe energy absorption. Measured energy intake was 23–85 kcal/kg/day, and 81% had hyperphagia that was not braked by the presence of PN.[4] The mechanisms behind AH have not been described beyond observation of the behavior and its relationship to PN energy need.

The gastrointestinal PYY ghrelin (GHR) has strong orexigenic effects on eating behaviors. Approximately two-thirds of the PYY is secreted by the stomach and one-third by the small intestine.[5] Plasma GHR concentration is highest in the fasting state and drops within 1 hour of a meal.[5] In addition to this orexigenic role around meal ingestion, GHR plays a hormonal role in the regulation of body fat. GHR concentration is increased up to 3-fold during malnutrition (usually anorexia nervosa models), increased with weight loss, and decreased with obesity and weight gain.[6]

In contrast to GHR, PYY is secreted by the distal small intestine and colon in response to chyme in the bowel lumen, with anorexigenic effects on eating behavior.[5] PYY concentration is increased at the end of a meal and remains elevated for several hours. PYY secretion varies with the size of the meal, and concentrations are highest after the largest evening meal. PYY is also recognized as the mediator of the intestinal brake response, where fat in the distal small intestine triggers a slowing of transit in the proximal small intestine.[7,8]

The purpose of this article was to determine whether GHR or PYY concentration could explain the phenomenon of AH in patients with SBS, as well as to evaluate any association of GHR with BMI.

Methods

Participants

Included study participants were nonpregnant adults older than 18 years of age with a diagnosis of surgical SBS for ≥2 years' duration (to ensure that intestinal adaptation had already occurred) and a current or recent history of PN support. Patients were obtained primarily from the home PN population managed by the Clinical Nutrition Support Service of the University of Pennsylvania Health System.

Patients were excluded from the trial if they had a new cancer diagnosis (other than skin cancer) within the past 5 years, renal insufficiency (creatinine >2 mg/dL), or a primary

diagnosis other than SBS that required their PN support. In addition, patients with end jejunostomy anatomy or gastric resection were not included.

The protocol for the study was approved by the Institutional Review Board of the University of Pennsylvania and by the Advisory Committee of the General Clinical Research Center (GCRC). All participants gave informed consent for participation.

Study Design

The enrolled patients participated in a double-blind, random-order, placebo-controlled pilot evaluation of the impact of oral oleic acid supplements on transit time and nutrient absorption. The results from this main study are under review. Eight patients were enrolled, and 1 dropped out after a single dose of the placebo supplement, leaving complete data on 7 participants. The data presented here are from the 2 baseline visits (no supplement treatment) that occurred at approximately 6-month intervals. Patients were admitted to the GCRC for 48-hour stays to enable data collection.

Body weight was measured to the nearest 0.1 kg in light clothing without shoes using a calibrated digital scale. Height was measured to the nearest cm with a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight(kg)/height(cm)^2.

Nutrient Balance Tests

Nutrient absorption was measured by classical nutrient balance studies during 48-hour admissions to the GCRC. Patients were encouraged to select meals that replicated their usual food intake at home. For the balance studies, a duplicate aliquot of all food and fluid intake offered to the patient and a second sample of food not taken by the patient were collected, kept under refrigeration, blended, and frozen at −80°C. A complete collection of all fecal or ostomy output during the 48-hour admission was weighed and timed as passed, blended, and frozen. These frozen samples were assayed for energy content by bomb calorimetry[9] at Covance Laboratories, Inc (Madison, WI). Energy absorption was calculated as energy intake (energy given – energy not taken) – energy excretion (stool output) in kcal/day. An a priori definition of AH of 40 kcal/kg energy intake was used for analysis.

Assays

A 10-mL tube of blood was drawn in the fasting state during each visit to the GCRC and treated with aprotinin, and serum was frozen at −80°C until assay. Samples were assayed in duplicate by radioimmunoassay for GHR and total human PYY (PYY1–36 and 3–36) using kits by Linco Research, Inc (St. Charles, MO). These methods achieve sensitivity of 10 pg/mL when a 100-μL serum or plasma sample is incubated at 4°C in a 2-day disequilibrium assay.

Statistical Analysis

Data are presented as median (range) for clinical descriptions and mean ± SD for PYY concentrations. Pearson correlations were used to evaluate relationships between GHR and PYY concentrations, BMI, and energy intake and absorption. SPSS 13.0 (SPSS, Inc,

Chicago, IL) was used for analyses. A probability of <.05 was considered statistically significant.

Results

Clinical data are given in Table 1. The study participants had a median age of 62 (range, 45–66) years and time since initial SBS of 6.6 (range, 2–29) years. BMI was normal in 5 and overweight in 2 patients; median BMI was 21.2 (range, 19–27.7) kg/m^2. Although all patients had started with full PN at 100% of needs, by this observation time, only 1 individual still required this level of feeding, 5 depended on infusion of at least biweekly fluid and electrolytes, and 2 were not dependent on infusions (Table 2). The median remaining small bowel length was 85 (range, 25–150) cm, and the remaining colon in continuity varied from none in 2 patients to approximately 50% in 3 patients, and more than 50% in the remaining 3 patients. Only 2 patients had an intact ileocecal valve.

Energy intake and absorption data, as well as GHR and PYY concentrations, are given in Table 2. Five of the 7 participants had AH based on their measured energy intake of >40 kcal/kg/day, and the mean intake was 49.7 ± 17.1 kcal/kg/day. Energy actually absorbed was variable but considerably less than intake in all participants, and the mean energy absorption was 31.5 ± 7.5 kcal/kg/day. In addition to this oral intake, 4 participants infused PN kcal at a mean intake of 618.6 kcal, 43.6 g of amino acids, 3 days/week. The mean plasma GHR concentration was 1130.2 ± 193.2 pg/mL, and PYY was 242.1 ± 177.2 pg/mL.

Neither GHR nor PYY was significantly related to energy intake or absorption (Table 3). BMI trended toward an inverse relationship with GHR ($R = -0.540$, $P = .211$). Length of the remaining short bowel was not significantly related to either GHR or PYY nor were the PYY different by the presence of AH or PN dependence.

Discussion

Rigorous AH was demonstrated in these patients with severe SBS, but the AH was not related to fasting GHR or PYY concentration. BMI trended toward an inverse association with GHR, even in this small group of participants with a narrow range of BMI.

Little is known about GHR in patients with SBS. In a case series of 24 malnourished patients (BMI = 19.9 kg/m^2) with SBS in the Czech Republic, fasting GHR concentration was actually significantly less than healthy control participants.[10] The authors suggested that, because their participants had no gastric resections, the most likely explanation for these low GHR concentrations was limited secretion from the remaining small intestine. The limited remaining short bowel in these current study participants who also did not have gastric resection seems a likely explanation for these measured Gl PYY concentrations.

In an attempt to evaluate the influence of PN infusions on Gl PYY concentrations and appetite, 6 home PN patients were studied in a crossover design over 2 hours after infusion of 10% dextrose, 10% lipid, or PN with dextrose and amino acids.[11] Infusion of glucose or PN actually reduced GHR concentration, and lipid did not. The lipid infusion was associated with reduced PYY that returned to preinfusion concentration by the end of the 2-hour study.

Our fasting GHR and PYY were drawn in the morning after no overnight infusion and prior to a meal and thus should not have been affected by infusion. In addition, the actual energy infusion in these patients was very limited (approximately 600 kcal/day). The range of GHR concentration in this study at baseline was 900–1100 pmol/L and similar to our data.

Our study participants had a median age of 62 years, and thus a possible influence of age on PYY secretion was considered. A group of older (age ≥70 years) adults was compared with those ages 18–35 years for GHR response to acute weight loss by an energy-restricted diet.[12] There was no difference in plasma GHR concentration measured over 24 hours between the 2 groups either before or after energy restriction, suggesting that aging does not affect GHR secretion.

The trend toward an inverse correlation of fasting plasma GHR concentration with BMI in this small group of participants was in the direction reported by others in participants over a broad range of body weight and weight stability conditions.[5,6,12] The fact that this relationship holds despite the limited range of BMI in these study participants (19–27.7 kg/m^2) and their weight was not changed during the time of study suggests that GHR secretion might have a role to play in body fat stability. Most of these participants were heavier when their SBS first occurred, but the weights during this period of study and PN energy requirements had been stable for years.

The actual food intake in this group of patients is similar to the group from France, and the presence of parenteral energy intake did not seem to limit oral food intake.[5] In fact, the PN energy had been gradually reduced over time in response to slow weight gain in patients as their absorbed energy from dietary sources increased. Several years after their initial SBS, these patients had very limited PN energy supply and relied on hyperphagic oral intake to maintain their weight. The French group also noted an increase in energy intake in patients who were more than 6 months after their initial SBS resection.[5] This current group of patients was so far past that early time window that they may have been fully established in terms of hyperphagia. Their intake may well have been considerably less in the early days after SBS.

There were several limitations to the study. The number of participants who were enrolled in this pilot study was very small, and thus the study may have been underpowered to detect any subtle association of GHR or PYY on AH or BMI. The patients also had variable degrees of SBS, if judged by their PN dependence and their length of remaining intestine. In a group with more diverse Gl disease burden, it is more difficult to observe significant findings due to the wide standard deviations in outcome measures. The admissions for energy balance studies were 2 days, rather than the 3 or 4 days typically employed in healthy control participants. Because we did not change their dietary patterns from their typical intake at home, and furthermore they experienced rapid transit of foodstuffs through their intestine due to SBS, longer times for observation for nutrient balance may have had limited advantage but considerable patient burden. In these study participants, the standard deviation of GHR concentration was actually <20% of the mean concentration, although PYY, energy intake, and energy absorption were considerably more variable. A further limitation was our inability to measure these Gl PYY in conditions other than fasting. For GHR, the fasting

concentration would be most predictive of eating behavior, but PYY levels increase more after the meal and continue to be elevated for some time. Because both PYY concentrations were relatively low in the fasting state, however, these patients may not have been able to secrete significantly higher concentrations in response to diet. A stronger study design would also measure these same PYY concentrations in healthy control participants, but our protocol did not accommodate this measurement.

Conclusions

The rigorous adaptive hyperphagia measured in these patients with SBS was not related to fasting GHR or PYY, suggesting the need to explore other mechanisms for this behavioral outcome. BMI, as a surrogate for body fat stores, trended toward an inverse association with GHR concentration as expected, even though these patients were within a near-normal weight range.

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Table 1

Demographic and Clinical Data

	Age, y/Sex	BMI, kg/m^2	Cause of SBS	SBS, y	Small Bowel Length, cm	Colon
1	65/F	19	Cervical cancer Radiation Enteritis	7.8	120	None
2	65/F	22.1	Ulcerative colitis Resection	7.3	60	None
3	45/M	27.7	Crohn’ s disease Resections	3.8	70	50-cm transverse colostomy
4	66/M	23.5	Mesenteric vein infarction	2.9	52; ileal fistula	Right hemi-colectomy
5	59/F	21.8	Mesenteric vein infarction	5	100	Right hemi-colectomy
6	65/F	19.6	Mesenteric vein infarction	12.5	25	>50% colon
7	42/F	21.6	Adhesiolysis Ischemic stricturoplasty	2	100	Ileocecal valve + entire colon
8	59/M	26.2	Crohn’ s disease Resections	29	150	Ileocecal valve + entire colon

M, male; F, female; BMI, body mass index; SBS, short bowel syndrome.

Table 2

Energy Intake and Absorption vs Plasma GHR and PYY Concentration

Participant	Dietary Energy Intake, kcal/kg	Dietary Energy Absorption, kcal/kg	Parenteral Nutrition, kcal/Amino Acid, g Per Infusion	Infusions Per Week	GHR, pg/mL	PYY, pg/mL
1	73.14	32.15	740/60	7	1507.62	80.17
3	50.53	28.13	0/0	3	941.36	106.2
4	24.95	19.22	1540/80	4	1254.22	304.68
5	50.68	39.71	1450/65	5	1000.69	178.2
6	68.37	28.02	600/100	2	1035.52	563.79
7	35.31	32.18	0/0	0	1106.45	104.14
8	44.64	41.18	0/0	0	1065.46	357.28
Mean	49.66	31.51	618.6/43.6	3	1130.189	242.0657
SD	17.05	7.49	671.2/42.7	2.6	193.2097	177.235

Table 3

Correlation Coefficients Between Study Variables by Pearson's Correlation

	Energy Intake	Energy Absorbed	Body Mass Index	Short Bowel Length
GHR	+0.22	−0.23	−0.54	+0.19
PYY	+0.10	−0.13	+0.12	−0.45