Resection of the Large Bowel Suppresses Hunger and Food Intake and Modulates Gastrointestinal Fermentation

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Objective: To assess appetite and gut hormone levels in patients following partial (PR) or total resection (TR) of the large bowel.

Methods: A comparative cross sectional study was carried out with healthy controls ($n = 99$) and patients who had undergone PR ($n = 64$) or TR ($n = 12$) of the large bowel. Participants consumed a standard (720 kcal) breakfast meal at 0830 ($t = 0$) h followed by lactulose (15 g) and a buffet lunch ($t = 210$ min). Participants rated the subjective feelings of hunger at $t = -30$, 0, 30, 60, 120, and 180 min. Breath hydrogen (BH) concentrations were also evaluated. In a matched subset (11 controls, 11 PR and 9 TR patients) PYY and GLP-1 concentrations were measured following breakfast. The primary outcome measure was appetite, as measured using visual analogue scales and the buffet lunch. The secondary outcome was BH concentrations following a test meal.

Results: PR and TR participants had lower hunger and energy intake at the buffet lunch meal compared to controls. PR subjects had higher BH concentrations compared to controls and TR subjects. BH levels correlated with circulating GLP-1 levels at specific time points.

Conclusions: PR or TR of the large bowel reduced feelings of hunger and energy intake, and PR increased gastrointestinal fermentation.

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Introduction

Obesity is a major international health issue (1). Understanding how food intake is regulated is important to facilitate dietary, pharmacological, and behavioral interventions to reduce weight gain or promote weight loss. Appetite is regulated by a complex system of central neuronal circuits which modulates energy homeostasis in response to neural and endocrine signals from the periphery (2). Specific hormones released from the gastrointestinal tract are known to play a role in appetite regulation (3). The peptide hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) are released from the L cells of the gastrointestinal tract following a meal and are thought to act as signals of satiety and satiation (4). The density of L cells increases distally in the gastrointestinal tract, with increased density in the ileum compared to the proximal small intestine, and the largest concentration is found in the large bowel (5). The L cell expresses a large number of G protein coupled nutrient receptors, and studies have suggested that specific macronutrients can modulate the release of PYY and GLP-1 (6,7). Animal and human studies have suggested a causal relationship between products of fermentation in the gut and circulating gut hormone levels. Gut micro-organisms are thought to ferment complex carbohydrates entering the colon to generate short chain fatty acids (SCFA), which can stimulate PYY and GLP-1 release (8,9).

The postprandial signaling that stimulates the release of anorectic gut hormones is complex. PYY and GLP-1 are released within 30 min of consuming a meal, before nutrients reach the regions of the gut with the highest levels of PYY and GLP-1 expression. Hormonal or neuronal factors may signal from the upper gastrointestinal tract to L cells lower down the gut to stimulate the release of GLP-1 and PYY. It is also possible that the low levels of GLP-1 present in the upper intestine are the source of the early postprandial increase in circulating GLP-1 levels (10).

Understanding how L cell function is regulated may allow such systems to be exploited to prevent or treat obesity. Investigating

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appetite and gut hormone release in patients who have had portions of their gastrointestinal tract removed may provide useful information regarding the factors regulating hunger and satiety and the source of circulating gut hormones. We hypothesized that appetite, gut fermentation, and gut hormone levels would be altered in patients who had undergone partial or total removal of the large bowel compared to healthy controls.

Methods

Ethical approval was obtained from the Ethical Review Committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka (Application No: A128). All volunteers gave written informed consent.

Subjects

Ninety-nine healthy controls (55 male, 44 female) and 76 subjects (36 male, 40 female) who had undergone large bowel resection were recruited from surgical units of the Colombo North Teaching Hospitals and the Colombo South Teaching Hospital in Sri Lanka. Those with a history of intestinal surgery or disorders of the intestinal tract (colitis, irritable bowel) were excluded from being controls. Subjects who underwent surgery for large bowel cancer were free of cancer based on clinical (normal performance status according to WHO criteria), biochemical (basic blood parameters, stools for occult blood, carcinoembryonic antigen within normal limits), and radiological assessment (chest X-ray, US scan abdomen and colonoscopy normal) at the time of recruitment to the study (11). Those with chronic illness (e.g., diabetes mellitus, Parkinson's disease), those who had undergone irradiation, and subjects on long-term medication since resection were excluded from the study (12,13). Those who had undergone large bowel resection were classed as either partial resection (PR) (64 subjects, 33 males, 31 females) for those who had undergone subtotal/hemi-colectomy, abdominoperineal resection (APR), low anterior resection (LAR), high anterior resection (HAR), or anterior resection (AR) or as total resection (TR) (12 subjects, 3 males, 9 females) for those who had undergone TR of the large bowel, including both the colon and the rectum.

Study protocol

Subjects who had undergone large bowel resection attended the skills laboratories of the professorial surgical units at the Colombo South Teaching Hospital and the Colombo North Teaching Hospital. Controls attended the Department of Physiology, University of Sri Jayewardenepura.

The study commenced at 0800 h following a 10-h overnight fast, during which only water was permitted to be consumed. Subjects were asked to refrain from smoking, alcohol consumption, and exercise during the preceding 24 h. On arrival, a cannula was placed in a subset of 31 participants' forearms to allow blood samples to be taken.

Meal test

All participants consumed a standard 720 kcal breakfast meal containing 50 g fat, 50 g carbohydrate, and 32.9 g protein and consisting of bread (70 g), butter (30 g), and curry and a cup of tea with 12 g sugar without milk at 0830 h. Lactulose (15 g) was given immediately after the standard breakfast. At 210 min after breakfast, all participants were given a buffet lunch in excess. Lunch comprised rice, lentils, tuna fish, eggplant, and a salad, while dessert was a standard 80 g cup of vanilla ice cream. All participants were asked to eat until they were comfortably full. Each component of the lunch meal was weighed before and after eating and the energy intake calculated using the diet plan 5 (dietary analysis Software-Forestfield software Ltd., West Sussex, UK) which is based on McCance and Widdowson's composition of food (14).

Appetite assessment

Participants rated subjective feelings of hunger ("How hungry do you feel right now?"), pleasantness to eat ("How pleasant would it be to eat right now?"), prospective food intake ("How much could you eat right now?"), fullness ("How full do you feel right now?"), and sickness ("How sick do you feel right now?") using 100 mm horizontal visual analogue scales (VAS) at −30, 60, 120, and 180 min following the breakfast (15). They were also asked to rate the tastiness, pleasantness, and palatability of the breakfast immediately after they had finished it.

Breath hydrogen

Breath hydrogen (BH) concentrations were evaluated as a measure of colonic fermentation before breakfast (−30 min) and at 60-min intervals up to 180 min after breakfast, using a portable BH monitor (Bedfont EC60 Gastrolizer BSEN ISO9001, Rochester, Kent, UK) with a sensor sensitivity of 1 ppm (parts per million). A BH concentration of more than 10 ppm was considered a positive result (16).

Gut hormone analysis

Plasma PYY and GLP-1 concentrations were measured at −30, 60, 120, and 180 min after breakfast in a subset of 31 age-, sex-, and body mass index (BMI) -matched subjects (11 controls, 11 PR, 9 TR) using in-house radioimmunoassay (17,18). The detection limit for PYY was 10 pmol/l and the intra- and inter-assay variation was 6.0% and 9.5%, respectively. The detection limit for GLP-1 was 2 pmol/l and the intra- and inter-assay variation was 8.7% and 8.0%, respectively.

Statistical analysis

Variables of control, PR, and TR participants were compared using regression analysis followed by *post hoc* analysis using the Dunnett's test. Hunger, pleasantness to eat, prospective food intake, fullness, sickness, PYY and GLP-1 concentrations, BH concentration, and changes in hunger levels compared to −30 min (baseline) between groups at different time points were compared by regression analysis followed by *post hoc* analysis using the Dunnett's test. Pearson correlation coefficients were used to assess associations between other parameters, PYY and GLP-1 concentrations, and incremental area under the curve (IAUC) for the PYY and GLP-1 responses. Tastiness, pleasantness, and palatability of the breakfast were assessed immediately after breakfast and lunch. All analyses were performed using SPSS software (version 16). Significance was assigned to a P value of <0.05.

TABLE 1 Characteristics of the subjects by type of surgery

	HC (male $n = 55$, female $n = 44$)	PR subjects (male $n = 33$, female $n = 31$)	TR subjects (male $n = 3$, female $n = 9$)
Mean age ± SD (years)			
Male	42.1 ± 12.7	59.2 ± 12.6	38.7 ± 17.2
Female	48.3 ± 12.8	54.7 ± 13.5	40.0 ± 11.02
Mean BMI ± SD (kg/m^2)			
Male	21.7 ± 4.0	22.4 ± 2.9	24.2 ± 0.6
Female	22.8 ± 3.8	22.8 ± 4.2	20.3 ± 2.4
Sub-cohort of subjects and controls in whom gut hormones were assayed			
	Control (male $n = 3$, female $n = 8$)	PR subjects (male $n = 1$, female $n = 10$)	TR subjects (male $n = 3$, female $n = 6$)
Mean age ± SD (years)			
Male	41.7 ± 17.7	49.8	38.7 ± 17.2
Female	41.9 ± 11	40.5 ± 13.0	40.2 ± 13.4
Mean BMI ± SD (kg/m^2)			
Male	26.9 ± 4.0	25.0	24.2 ± 0.6
Female	23.2 ± 4.5	21.9 ± 4.4	20.2 ± 2.1

HC, healthy controls; PR, patients who had undergone partial resection of the large bowel; TR, patients who had undergone total resection of the large bowel; SD, standard deviation.

Results

Demographic and anthropometric assessment

The age and BMI of the three participant groups are shown in Table 1. There were no significant differences in age or BMI between any of the groups examined. The type of surgical procedure, diagnosis, and the average time since surgery when investigated for the PR and TR groups are shown in Table 2.

Visual analogue assessment of appetite

The subjective feeling of hunger was significantly lower ($P < 0.05$) in PR subjects at baseline (time point −30 min), and in both PR ($P = 0.001$) and in TR ($P < 0.05$) subjects at 180 min, compared to controls (Figure 1A). There were no significant differences between the groups regarding the change from baseline (−30 min) in the subjective feeling of hunger ratings following the breakfast (Figure 1B).

There was a significant reduction in the estimate of prospective food intake in PR subjects ($P < 0.05$) at 60 min and in PR ($P = 0.001$) and TR ($P < 0.05$) subjects at 180 min (Figure 1C). There were no significant differences between the groups regarding the change from baseline (−30 min) in the estimate of prospective food intake following the breakfast (Figure 1D).

PR ($P = 0.016$) and TR subjects ($P = 0.031$) had a significantly lower feeling of pleasantness to eat at 180 min (Figure 1E). There were no significant differences between the groups regarding the

TABLE 2 Surgical procedure, diagnosis, and average time since surgery in subjects who underwent partial resection (PR) or total resection (TR) of the large bowel

Type of the surgical procedure	Diagnosis	Average time (years) since surgery to date of investigation (approximate length of the bowel segment removed)
Anterior resection[a] ($n = 26$)	Carcinoma rectum	2.6 (15–20 cm)
Abdominoperineal resection[a] ($n = 11$)	Carcinoma rectum	2.7 (15–20 cm)
Hemi-colectomy[a] ($n = 13$)	Carcinoma colon	3.0 (35–50 cm)
Sigmoid colectomy[a] ($n = 7$)	Sigmoid colon carcinoma	1.8 (30–40 cm)
Subtotal colectomy[a] ($n = 5$)	Carcinoma colon	2.8 (135 cm)
Hartmans surgery[a] ($n = 2$)	Carcinoma rectum	4.0 (20 cm)
Proctocolectomy[b] ($n = 12$)	Familial adenomatous polyposis	2.8 (150 cm)

[a]Referred to as PR subjects.
[b]Referred to as TR subjects.

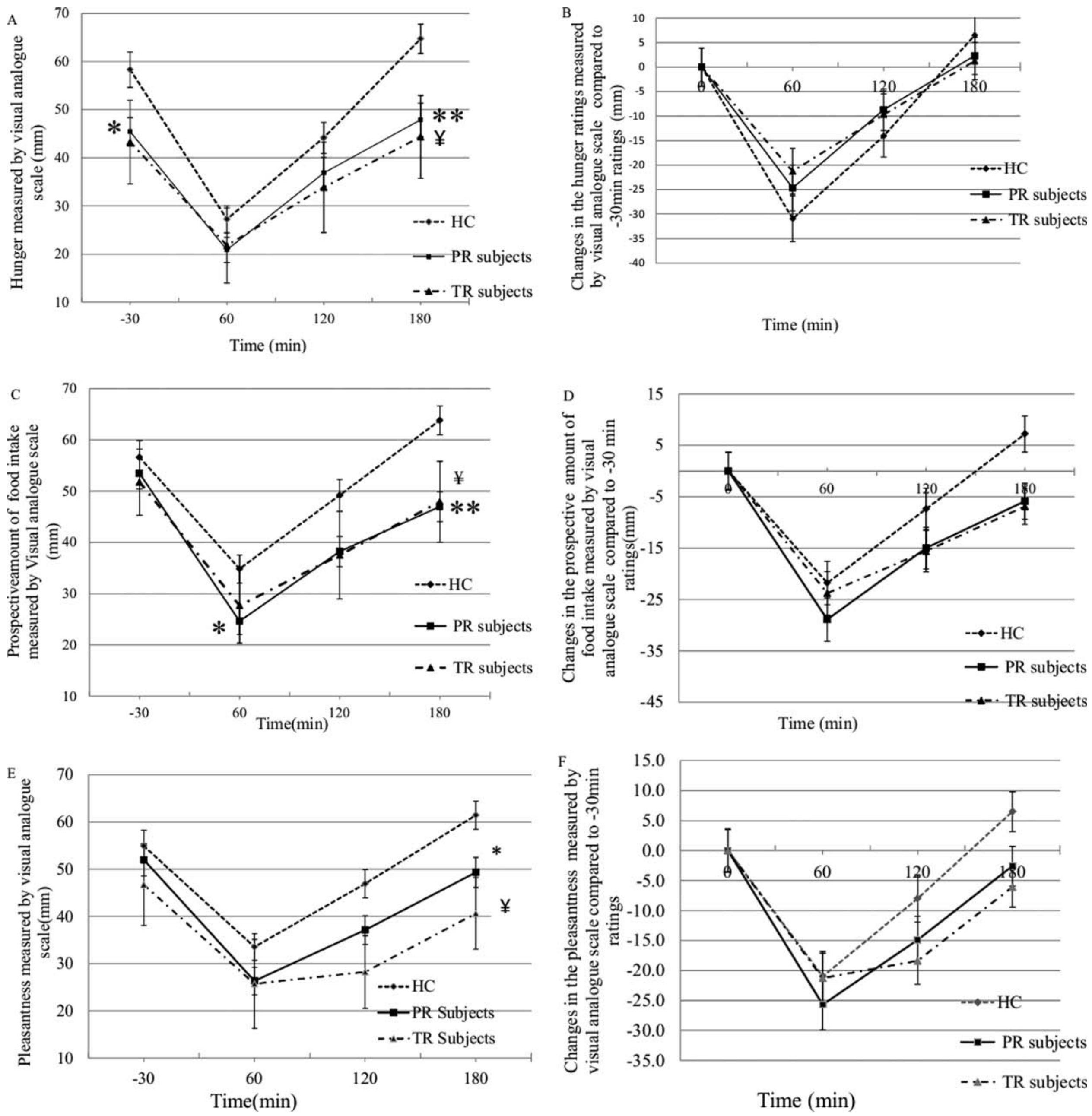

Figure 1 Subjective feelings of hunger, shown as (**A**) absolute values and (**B**) change from baseline, prospective amount of food intake, shown as (**C**) absolute values and (**D**) change from baseline, and pleasantness to eat, shown as (**E**) absolute values and (**F**) change from baseline, measured by 100 mm horizontal visual analogue scale in healthy controls (HC, $n = 99$), those who had undergone subtotal/hemi-colectomy, abdominoperineal resection, low anterior resection, high anterior resection, or anterior resection (PR, $n = 64$), and those who had undergone total resection of the large bowel, including both colon and the rectum (TR, $n = 12$). The subjective feelings of hunger ratings were indicated at −30, 60, 120, and 180 min following the breakfast. *$P < 0.05$, **$P < 0.001$. PR vs. HC; $^{¥}P < 0.05$. TR vs. HC. All data expressed as mean ± SEM.

change from baseline (−30 min) in the feeling of pleasantness to eat following the breakfast (Figure 1F).

There was no significant difference in the subjective feelings of fullness or sickness between control, PR, or TR participants at any time point (Table 3). There was a significant reduction in the perception of tastiness ($P = 0.001$) and pleasantness ($P = 0.005$) of the breakfast in the PR subjects compared to controls (Figure 2A). However, there was no significant difference in the perception of taste and palatability of the buffet meals between groups (Table 4).

Energy intake at a buffet meal

The energy intake (mean ± SD (kcal)) at the buffet lunch meal was significantly lower in subjects who had undergone PR or TR compared to controls (Figure 2B) (controls, 759.719 ± 216.848;

TABLE 3 Feeling of fullness and sickness measured by the visual analogue scale

	HC ($n = 98$)		PR subjects ($n = 64$)		TR subjects ($n = 12$)	
Time points (min)	Mean	SD	Mean	SD	Mean	SD
Feeling of sickness (mm)						
−30	16.9	8.1	8.8	12.5	18.8	9.9
60	14.9	7.5	15.1	7.6	10.8	6.9
120	12.9	6.3	17.4	7.0	19.8	8.6
180	13.8	6.2	18.3	9.3	21.8	10.1
Feeling of fullness (mm)						
−30	17.2	11.3	24.6	17.2	23.8	16.2
60	56.0	28.5	57.1	25.9	51,7	29.7
120	42.0	26.9	45.3	22.0	36.7	32.1
180	30.9	28.4	35.9	25.0	44.2	30.7

HC, healthy controls; PR, patients who had undergone partial resection of the large bowel; TR, patients who had undergone total resection of the large bowel; SD, standard deviation.

PR, 581.063 ± 213.065, $P < 0.001$; TR, 529.667 ± 151.693, $P < 0.005$).

BH concentration levels

PR subjects had significantly higher BH levels than those of controls and TR subjects at 60 min ($P < 0.05$) and at 120 min ($P < 0.05$) (Table 5). TR subjects had a significantly lower postprandial BH level ($P < 0.05$) (Table 5).

Gut hormones

The demographic details of the sub-cohort in which gut hormones were measured are presented in Table 1. There was a trend for higher postprandial circulating GLP-1 concentrations in TR and particularly in PR subjects, though not statistically significant, and a trend for lower PYY levels in the TR subjects (Figure 3A). The IAUC for change in PYY levels from baseline was significantly higher in TR subjects between −30 and 60 min compared to controls ($P < 0.05$) (Figure 3B). There was no significant difference in the IAUC for GLP-1 concentration between the study groups (Figure 3C).

In PR subjects, hunger levels at 180 min negatively correlated with PYY concentrations at −30 min ($r = -0.783$, $P = 0.004$), at 60 min ($r = -0.667$, $P = 0.024$), and at 120 min ($r = -0.601$, $P = 0.050$). The IAUC for change in GLP-1 levels between −30 and 60 min correlated with BH concentration levels at −30 min ($r = 0.785$, $P = 0.004$), at 60 min ($r = 0.677$, $P = 0.022$), and at 180 min ($r = 0.597$, $P = 0.052$) in PR subjects.

The BH concentration increase observed coincides with the increase in GLP-1 concentration at 60 min and at 120 min, and the fullness levels at 60 min correlate with the BH concentrations at 60 min ($r = 0.715$, $P = 0.03$), at 120 min ($r = 0.83$, $P = 0.005$), and at 180

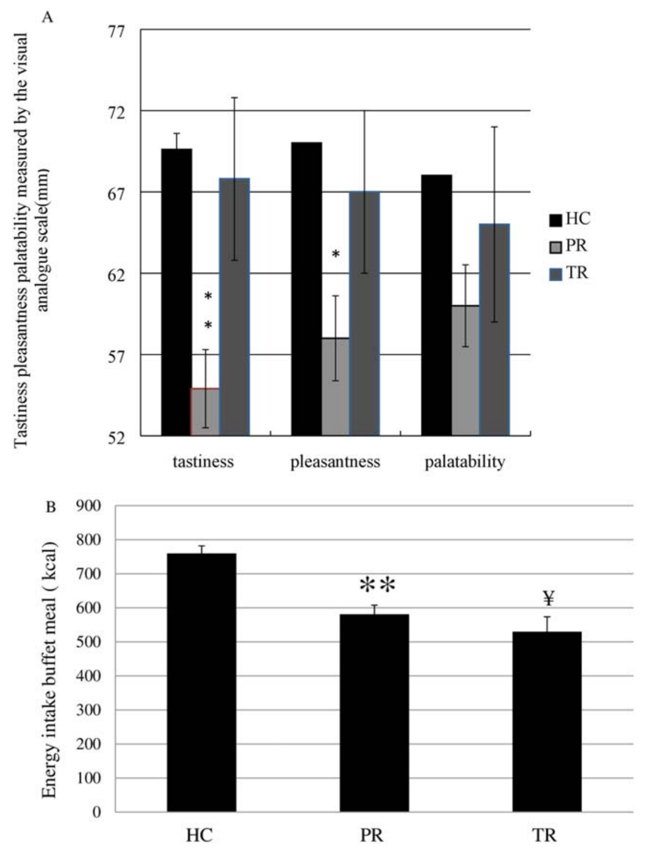

Figure 2 (**A**) Tastiness, pleasantness to eat, and palatability of breakfast meal assessed immediately after the breakfast meal by 100 mm horizontal visual analogue scale in healthy controls (HC, $n = 99$), those who had undergone subtotal/hemi-colectomy, abdominoperineal resection, low anterior resection, high anterior resection, or anterior resection (PR, $n = 64$), and those who had undergone total resection of the large bowel, including both colon and the rectum (TR, $n = 12$). $^*P < 0.05$, $^{**}P < 0.001$ for PR vs. HC. All data expressed as mean ± SEM. (**B**) The energy intake of HC ($n = 99$) and PR ($n = 64$) and TR ($n = 12$) subjects at a buffet lunch in excess. $^{**}P < 0.01$ for PR *vs*. HC; $^{¥}P < 0.05$ for TR vs. HC. All data expressed as mean ± SEM. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 4 Taste, pleasantness, and palatability of the buffet meal measured on a visual analogue scale (mm)

	HC ($n = 95$)		PR subjects ($n = 64$)		TR subjects ($n = 12$)	
	Mean	SD	Mean	SD	Mean	SD
Taste (mm)	69.6	27.6	54.9	19.2	67.8	18.1
Pleasantness (mm)	74.0	23.1	71.2	22.5	69.8	25.9
Palatability (mm)	72.4	23.7	72.5	18.1	65.1	23.4

HC, healthy controls; PR, patients who had undergone partial resection of the large bowel; TR, patients who had undergone total resection of the large bowel; SD, standard deviation.

TABLE 5 Breath hydrogen (BH) levels and incremental area under the curve (IAUC) at different time points

	HC ($n = 92$)		PR subjects ($n = 55$)		TR subjects ($n = 12$)		*P* value	
Time points	Mean	SD	Mean	SD	Mean	SD	PR subjects	TR subjects
Breath hydrogen concentrations (ppm)								
−30	8.9	11.3	10.7	17.4	4.7	5.4	0.17	0.35
60	8.1	9.1	10.4	14.4	8.3	9.3	0.05[a]	0.10
120	11.6	13.2	16.1	16.7	6.9	5.9	0.03[a]	017
180	18.0	17.2	18.3	18.9	10.3	11.4	0.51	0.10
IAUC of BH concentrations (ppm × min)								
−30 to 60 min	748.1	856.8	971.3	1350.5	497.9	440.6	0.42	0.05[a]
60–120 min	631.1	641.0	780.4	811.1	439.5	441.3	0.27	0.06
120–180 min	917.0	858.7	917.0	858.7	513.8	492.9	0.09	0.19
Total	2296.2	1982.1	2568.7	2761.70	1451.2	1299.9	0.17	0.04[a]

HC, healthy controls; PR, patients who had undergone partial resection of the large bowel; TR, patients who had undergone total resection of the large bowel; SD, standard deviation.
[a]Significantly different compared to controls.

min ($r = 0.742$, $P = 0.021$) in PR subjects. In PR subjects, the palatability of the breakfast meal negatively correlated with the GLP-1 concentration at −30 min ($r = -0.669$, $P = 0.49$).

Discussion

This study examined the effects of colectomy on appetite, energy intake, and gut fermentation and investigated the relationship between gut fermentation, gut hormone concentrations, and appetite in subjects who underwent PR or TR of the large bowel compared to healthy controls. Compared to other studies examining appetite in such patients (19-21), this study included a relatively large cohort of 64 PR and 12 TR subjects. The PR and TR participants had significantly lower subjective feelings of hunger and prospective food intake at specific time points and ate less at a buffet lunch meal compared to controls. BH levels of PR subjects were significantly higher compared to controls and TR subjects at specific time points, and the TR subjects had significantly lower postprandial BH production.

Reduction or total absence of the large bowel was associated with a reduction in food intake. This may be due to the absence of factors from the large bowel, or it may reflect changes to other parts of the gut such as the small intestine secondary to this loss of large bowel. Altered neurohumoral mechanisms may be responsible for the altered appetite observed (22-24). It is interesting that there was a trend for postprandial GLP-1 levels to be higher in PR and TR subjects, but a similar pattern was not observed in PYY levels. The upper small intestine expresses more GLP-1 than PYY and has numerous cells that express GLP-1 but not PYY (25). The areas of the gut responsible for the release of PYY and GLP-1 following a meal are unclear, but these studies suggest that the gut is able to maintain its release of GLP-1 following the loss of part or the whole of the colon. Perhaps the small intestine GLP-1 system is more elastic and able to respond to changes in the gut more readily than the PYY system. The ileum also contains a number of GLP-1 and PYY expressing cells, and it may be that the ileum increases its number and/or activity of L cells in response to the loss of the colon (26,27). This may represent a gut response to, for example, rapid small bowel transit following colectomy. Though PYY levels in TR subjects showed a trend to be lower than those in controls, it is interesting to note that they showed a relatively greater postprandial rise. It is possible that changes in PYY levels rather than absolute levels are important in appetite regulation; PYY levels and hunger ratings showed a negative association in PR subjects. The changes in gut hormones observed may be partly responsible for the difficulty in weight regain following colectomy. It is also interesting that the PR subjects rated the tastiness, pleasantness, and palatability of the breakfast as lower than the controls; there was also a trend for them to find the buffet meal less tasty, though this did not reach statistical significance. It may be that such effects influence food intake in the PR group, though they do not appear to drive the even greater reduction in food intake observed in the TR group.

BH is an indicator of bacterial fermentation in the gastrointestinal tract. It is interesting to note that although the TR subjects had the lowest BH levels, it is still detectable, suggesting some fermentation is occurring, presumably in the small intestine. Subjects who had undergone PR generally had higher levels of BH than control and TR subjects, implying a higher bowel fermentation that may reflect the remaining large bowel tissue responding to, and perhaps overcompensating for, the removal of the rest of the large bowel.

In PR subjects the IAUC for GLP-1 concentrations correlated with BH excretion at −30, 60, and 180 min. Recent animal and human studies have found fermentable food to stimulate the secretion of GLP-1 secretion (28-30). It is known that short chain fatty acids produced by fermentation of nondigestible carbohydrate in the colon can stimulate GLP-1 and PYY release (9). In this study, a standard meal containing lactulose was used to increase fermentation, in contrast to other studies in which a specific fermentable nutrient such as oligofructosacharide or beta glucan was used. Further work is

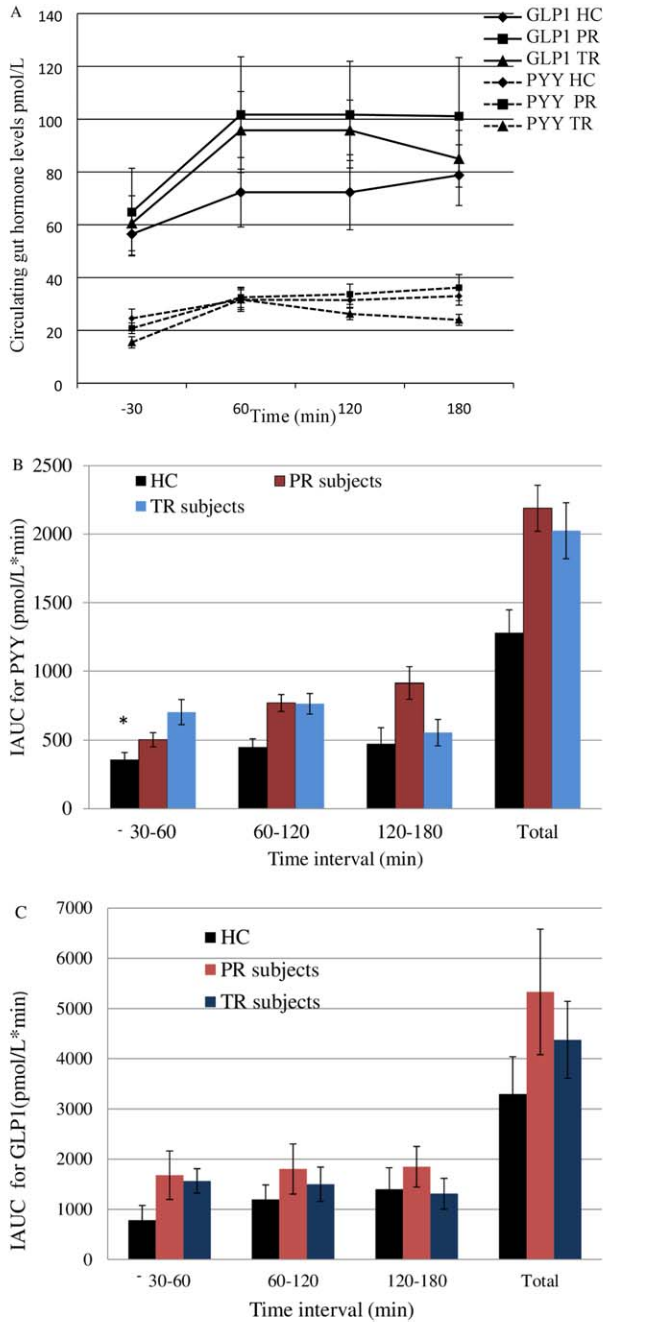

Figure 3 (**A**) Plasma PYY and GLP-1 concentrations at −30, 60, 120, and 180 min in healthy controls (HC) ($n = 11$) and partial resection (PR) ($n = 11$) and total resection (TR) ($n = 9$) subjects following a test breakfast. All data expressed as mean ± SEM. Incremental area under the curve (IAUC) values for changes in plasma (**B**) PYY and (**C**) GLP-1 concentrations in HC ($n = 11$) and PR ($n = 11$) and TR ($n = 9$) subjects following a test breakfast meal. $^{¥}P < 0.05$ for TR vs. HC. All data expressed as mean ± SEM. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

required to understand the relationship between fermentation in the gut and the release of gut hormones. However, it is interesting to speculate that manipulating gastrointestinal fermentation may be able to alter appetite in the absence of surgery.

These data suggest that partial or total removal of the colon may result in alterations to the gut endocrine system and that partial removal may be associated with greater gastrointestinal fermentation than in controls. Further work is required to determine the mechanisms which mediate the effects of PR or TR of the colon on appetite and food intake. **O**

Acknowledgments

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