Serum peptide YY in response to short-term overfeeding in young men\textsuperscript{1–3}

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ABSTRACT

Background: Peptide YY (PYY), a gut hormone that inhibits appetite, has been linked to the development of obesity.

Objective: This study investigated the nutritional regulation of PYY after 7 d of overfeeding (70\% above normal energy requirements) in normal-weight, overweight, and obese men.

Design: Sixty-nine men (aged 19–29 y) participated in the study. We analyzed the relation between fasting serum PYY before and after a 7-d overfeeding challenge in normal-weight, overweight, and obese men. In addition, we analyzed PYY with obesity-related phenotypes including weight, percentage body fat (measured by dual-energy X-ray absorptiometry), body mass index (BMI), total cholesterol, HDL, LDL, glucose, insulin, insulin resistance, and \(\beta\) cell function evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR) and \(\beta\) cell function (HOMA-\(\beta\)) at baseline and in response to the energy surplus.

Results: Fasting serum PYY concentrations at baseline were not significantly different between the normal-weight, overweight, and obese subjects on the basis of dual-energy X-ray absorptiometry or BMI. Although the PYY concentration significantly increased due to overfeeding, no differences were observed between adiposity statuses. In addition, basal PYY was negatively correlated with the changes of total cholesterol, HDL, and LDL in normal weight. In addition, the increase in PYY after overfeeding was positively correlated with HDL cholesterol and glucose in normal-weight subjects.

Conclusions: Our findings suggest that fasting PYY concentrations are not associated with adiposity status. Moreover, the 7-d overfeeding challenge significantly increased fasting PYY, which is likely a protective response to the positive energy balance. Am J Clin Nutr 2011;93:741–7.

INTRODUCTION

It has been documented that gut hormones influence appetite and play an integral part in maintaining energy homeostasis through gut-brain communication (1, 2). Peptide YY (PYY), a short 36 amino acid protein with structural homology to neuropeptide Y (NPY) and pancreatic peptide (PP), is a gut hormone that increases satiety and consequently decreases food intake (3). PYY is released from the mucosa in the ileum and colon of the gastrointestinal tract existing in a PYY\textsubscript{3–36} and PYY\textsubscript{1–36} form (4, 5). Both forms are physiologically active and decrease pancreatic secretions and suppress gastrointestinal motility (6). PYY secretion increases in response to food consumption and is positively correlated with the calorie content of meals (7–9). However, it is not currently clear whether PYY concentration is dependent on adiposity status or if it plays an important role in the development of obesity.

Most studies of PYY conducted to date were performed in rodents. It was initially observed that PYY concentrations decreased after a diet-induced obese state in mice, which suggests that altered PYY secretion is associated with the development of obesity (10, 11). In some human studies, endogenous PYY concentrations were found to be lower in obese subjects and inversely correlated with body mass index (BMI), which suggests that PYY deficiency may contribute to obesity (11–14). In addition, the infusion of PYY was found to decrease the appetite of both lean and obese subjects and to subsequently decrease food intake (5, 13). Taken together, these data suggest that individuals with a lower concentration of PYY, such as overweight/obese individuals, may have a weaker satiety signal, which subsequently leads to the overconsumption of food and weight gain. In contrast with these studies, many other studies in rodents (15) and humans with larger sample sizes (16–18) could not replicate the relation between PYY and adiposity status. The administration of PYY was also found to not have any effect on appetite or weight loss (15, 18). Currently, data regarding the role that PYY plays in determining adiposity status are contradictory. In addition, there is no data concerning the effect of a positive energy balance on PYY and the potential difference between normal-weight, overweight, and obese subjects.

Our laboratory and others have shown that changes in nutritional status, such as overfeeding, have major effects on adipose tissue metabolism (19, 20), circulating concentrations of adipokines (21), and gene expression profiles (22). A positive energy balance may also influence circulating concentrations of gut hormones, such as PYY, and subsequently affect appetite. Although recent studies have suggested that PYY plays an important role in energy homeostasis (6, 17), no study has yet investigated the regulation of PYY after a short-term positive energy challenge. The response of PYY to changes in nutritional

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status will provide insight regarding the potential role of this gut hormone in the development of obesity and in other related phenotypes, including insulin resistance and serum lipid profiles.

The objective of the present study was to investigate the role that PYY plays in the development of obesity by investigating 1) fasting serum PYY concentrations in normal-weight, overweight, and obese healthy young men at baseline before overfeeding; 2) the response of PYY to short-term overfeeding between different adiposity statuses; and 3) the correlations of PYY with phenotypes of insulin resistance, glucose, and lipid metabolism.

SUBJECTS AND METHODS

Subjects were recruited from an overfeeding study investigating the effects of a positive energy balance on endocrine factors and on indicators of glucose and lipid metabolism (19, 20, 22). A total of 69 young men were recruited from the city of St John’s (Newfoundland and Labrador, Canada) and the surrounding areas. Inclusion criteria were as follows: 1) male sex; 2) 19–29 y of age; 3) at least a third-generation Newfoundlander; 4) healthy, with no serious metabolic, cardiovascular, or endocrine disease; 5) no use of medication for lipid metabolism; 6) reported stable weight (±2.5 kg) in the previous 6 mo; and 7) willingness to abstain from any alcoholic or additional calorie-containing beverage consumption during the study period. No study participants took any drugs or medications throughout the duration of the study. Initial data collection for this study began in October 2003. This study was approved by The Human Investigations Committee for the Faculty of Medicine, Memorial University of Newfoundland and Labrador, St John’s, Canada. All subjects provided written informed consent.

Serum measurements

Fasting blood samples were obtained from all subjects before and after the completion of the overfeeding intervention. Serum was stored at −80°C for subsequent analyses. Whole PYY (Millipore Corporation Pharmaceuticals, Billerica, MA) concentrations were measured in duplicate with enzyme-linked immunosorbent assays (ELISAs). The intraassay variation ranged from 4.8% to 5.4%, and the interassay variation was 5.1%. The detection limit of the PYY ELISA kits used was 10 pg/mL for a sample size of 20 μL. Serum insulin concentrations were measured with the use of an immunoassay analyzer (Immulite; DPC, Los Angeles, CA). The homeostasis model assessment (HOMA) was used as a measure of insulin resistance \[ \text{HOMA-IR} = \text{insulin} \times \text{glucose} \div 22.5 \] and \( \beta \) cell function \[ \text{HOMA-β} = 20 \times \text{insulin} \times \text{glucose} - 3.51 \] (23).

Serum concentrations of glucose, triglycericcerols, HDL cholesterol and total cholesterol were measured with an Lx20 analyzer (Beckman Coulter Inc, Fullerton, CA). LDL cholesterol was calculated as total cholesterol – HDL cholesterol – (triglycericcerols/2.2). The LDL-cholesterol and HDL cholesterol calculation is reliable in the absence of severe hyperlipidemia.

Measurement of body composition

Height and weight measurements were collected and BMI was calculated. BMI was defined as weight divided by height squared (kg/m²). Percentage body fat (%BF), percentage trunk fat (%TF), and percentage android fat (%AF) were measured by using dual-energy X-ray absorptiometry (DXA; Lunar Prodigy; GE Medical Systems, Madison, WI). Measurements were performed on subjects in a supine position, after the removal of all metal accessories, as previously described by us (20, 24). Version 12.2 of the enCORE software package (GE Medical Systems) was used for DXA analysis. Subjects fasted for 12 h before the data were collected. All measurements were collected on the first day of data collection and 1 d after the 7-d overfeeding intervention.

Overfeeding protocol

A 7-d overfeeding protocol was chosen for this study to ensure that the intervention would induce metabolic changes. Participants consumed 70% more calories than their normal energy requirements (hypercaloric), which consisted of 15% protein, 35% fat, and 50% carbohydrates to mimic the common daily diet in North America. Baseline energy requirements were determined from three 24-h dietary recalls and a 30-d dietary inventory. The average daily caloric intake was as follows: energy (baseline: 2969 kcal; overfeeding: 5471 kcal), protein (baseline: 106 g; overfeeding: 178 g), carbohydrates (baseline: 394 g; overfeeding: 713 g), fiber (baseline: 19 g; overfeeding: 33 g), total fat (baseline: 105 g; overfeeding: 221 g), saturated fat (baseline: 38 g; overfeeding: 71 g), and cholesterol (baseline: 304 mg; overfeeding: 735 mg). Subjects were offered meals at 0900, 1200, and 1700 every day, and the energy values and macronutrient content of the food were measured by using FOOD PROCESSOR SQL software (version 9.5.0.0; ESHA Research, Salem, OR). The Actical physical activity monitor (Mini Mitter Co, Inc, Bend, OR) was used to determine total energy expenditure. Physical activity levels were controlled below 15% between the baseline and overfeeding periods. Full details of our overfeeding protocol were previously described, and all of the participants in this study were members of these studies (19, 20, 22). On average, subjects gained 2.4 ± 1.3 kg body weight, of which 43.2 ± 31.6% (0.830 ± 0.542 kg) was body fat.

Statistical analysis

Data are presented as means ± SDs unless otherwise stated. Before any statistical analysis was performed, data that were not normally distributed were logarithmically transformed (triglycericcerols, insulin, HOMA-IR, and HOMA-β) to approximate normal distribution. Subjects were classified on the basis of %BF as either normal weight (8–20.9%), overweight (21–25.9%), or obese (≥26%) according to criteria recommended by Bray (25). Statistical analyses were also performed according to BMI as normal weight (≤24.9), overweight (25.0–29.9) or obese (≥30) according to criteria of the World Health Organization (26). To further explore the relationship between PYY and body composition, participants were divided into tertiles according to baseline fasting serum PYY concentrations (pg/mL) as follows: low (bottom 33.3%), medium (middle 33.3%), and high (top 33.3%) PYY concentrations. The range of serum PYY for the low, medium, and high groups were 23.85–90.73, 97.69–131.36, and 133.52–347.52 pg/mL, respectively.

Differences in variables between the 3 adiposity groups in response to overfeeding were analyzed by using a mixed-model repeated two-factor analysis of variance (ANOVA). Baseline values between the 3 adiposity groups were analyzed by using a one-factor analysis of variance. The Bonferroni post hoc test
was run after the one-factor ANOVA and the 2-factor ANOVA, which showed a significant overfeeding × adiposity interaction ($P < 0.05$). Within-group analysis of the response to overfeeding was performed with a Student paired $t$ test on variables that showed a significant overfeeding × adiposity interaction effect. Pearson’s correlation analyses were performed to screen for potential factors related to fasting PYY concentrations followed by partial correlation analyses after age was controlled for. Bonferroni testing was applied to correct for multiple comparisons. Three correlation analyses were performed as follows: 1) PYY at baseline was compared with changes in all variables in response to overfeeding. SPSS software version 17.0 (SPSS Inc, Chicago, IL) was used for all analyses. Statistical analyses were 2-sided, and $P < 0.05$ was considered to be statistically significant.

RESULTS

Comparison of characteristics at baseline and in response to short-term overfeeding

Physical and biochemical characteristics of subjects at baseline are shown in Table 1. Differences in body composition, glucose, and lipid metabolism between normal-weight, overweight, and obese young healthy men were previously described by us (19, 20, 22). Fasting serum PYY concentrations at baseline for normal-weight (121.47 ± 60.8 pg/mL), overweight (109.90 ± 53.8 pg/mL), and obese (118.93 ± 56.54 pg/mL) subjects were not significantly different from one another. PYY concentrations were also analyzed according to BMI criteria when no significant differences were found (data not shown).

Changes in body composition and phenotypes of glucose metabolism and lipids in response to the 7-d overfeeding are also described in Table 1. Our 7-d positive energy challenge for normal-weight, overweight, and obese young healthy men significantly increased body composition, serum lipids, insulin resistance, and $\beta$ cell function. These findings were previously described by us as well (19, 20, 22). The only significant overfeeding × adiposity status interactions found from our analysis were for %BF and %TF, which indicated that normal-weight subjects experienced a greater significant increase in %BF than did overweight and obese subjects (Table 1). Regarding whole PYY, no significant difference in concentration was found between normal-weight, overweight, and obese young men after overfeeding ($P = 0.758$). However, the main effect of overfeeding was significant, which indicated that the PYY concentration increased significantly as a result of the 7-d positive energy challenge ($P = 0.013$).

### Table 1

| Physical and biochemical characteristics of subjects at baseline and in response to 7 d of overfeeding |
|---|---|---|
| | Normal weight ($n = 23$–$27$) | Overweight ($n = 14$) | Obese ($n = 23$–$28$) |
| | Before | After | Before | After | Before | After | Before | After |
| Age (y) | 23.72 ± 3.6 | NA | 21.97 ± 3.1 | NA | 23.24 ± 2.6 | NA |
| Height (cm) | 179.51 ± 6.4 | NA | 179.38 ± 4.6 | NA | 179.07 ± 6.8 | NA |
| Weight (kg)$^{2–4}$ | 72.39 ± 9.2 | 74.53 ± 9.6 | 77.81 ± 4.2 | 79.39 ± 4.3 | 93.01 ± 15.6 | 95.65 ± 16.0 |
| BMI (kg/m$^2$)$^{2–4}$ | 22.55 ± 2.6 | 23.23 ± 2.8 | 24.13 ± 1.3 | 24.63 ± 1.5 | 29.10 ± 4.9 | 29.93 ± 5.0 |
| Body fat (%)$^{3–5}$ | 14.63 ± 3.3 | 15.38 ± 3.4$^7$ | 22.54 ± 0.8 | 22.82 ± 1.1$^7$ | 31.51 ± 5.0 | 31.26 ± 4.7 |
| Trunk fat (%)$^{3–5}$ | 16.55 ± 3.6 | 17.52 ± 3.8$^7$ | 25.39 ± 1.8 | 25.79 ± 2.7 | 35.22 ± 5.4 | 34.89 ± 5.1 |
| Android fat (%)$^{3–5}$ | 19.01 ± 4.4 | 19.86 ± 4.9 | 28.84 ± 2.6 | 29.45 ± 2.7 | 40.47 ± 7.1 | 41.06 ± 6.7 |
| Total cholesterol (mmol/L)$^7$ | 4.39 ± 0.9 | 4.67 ± 0.8 | 4.63 ± 0.9 | 4.72 ± 1.1 | 4.56 ± 0.7 | 4.79 ± 0.8 |
| HDL cholesterol (mmol/L)$^7$ | 1.38 ± 0.3 | 1.47 ± 0.3 | 1.38 ± 0.3 | 1.43 ± 0.3 | 1.19 ± 0.2 | 1.31 ± 0.3 |
| LDL cholesterol (mmol/L) | 2.61 ± 0.7 | 2.67 ± 0.7 | 2.82 ± 0.7 | 2.83 ± 0.9 | 2.79 ± 0.7 | 2.79 ± 0.6 |
| Triglyceride (mmol/L)$^{3,4,8}$ | 0.90 ± 0.3 | 1.16 ± 0.8 | 0.92 ± 0.3 | 1.00 ± 0.5 | 1.37 ± 0.7 | 1.58 ± 0.9 |
| Glucose (mmol/L) | 4.97 ± 0.4 | 5.03 ± 0.5 | 5.03 ± 0.4 | 5.09 ± 0.6 | 5.28 ± 0.7 | 5.17 ± 0.5 |
| Insulin (pmol/L)$^{2–4}$ | 42.86 ± 23.5 | 62.98 ± 23.8 | 69.51 ± 69.16 | 88.85 ± 86.3 | 96.99 ± 91.8 | 111.97 ± 77.1 |
| HOMA-IR$^{2–4}$ | 1.39 ± 0.8 | 2.09 ± 0.9 | 2.35 ± 2.68 | 2.95 ± 2.9 | 3.51 ± 3.8 | 3.85 ± 2.9 |
| HOMA-%TF$^{2–4}$ | 83.32 ± 38.6 | 125.63 ± 49.4 | 120.21 ± 74.09 | 175.90 ± 163.6 | 147.49 ± 90.62 | 189.67 ± 103.4 |
| Peptide YY (pg/mL)$^7$ | 121.47 ± 60.8 | 148.44 ± 93.37 | 109.90 ± 53.8 | 119.49 ± 38.9 | 118.93 ± 56.54 | 156.47 ± 58.27 |

$^1$ All values are means ± SDs. HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-%TF, homeostasis model assessment of $\beta$ cell function; NA, not applicable. Subjects were classified on the basis of percentage body fat as normal weight (8–20%), overweight (21–25%), or obese (≥26%) according to criteria recommended by Bray (25). Adiposity status and response to overfeeding were analyzed by 2-factor mixed-model ANOVA (version 17.0; SPSS Inc, Chicago, IL) for repeated measures.

$^2$ Significant difference between normal-weight and obese subjects at baseline, $P < 0.05$ (one-factor ANOVA followed by Bonferroni correction).

$^3$ Significant difference due to overfeeding, $P < 0.05$ (2-factor mixed-model ANOVA).

$^4$ Significant difference due to adiposity status, $P < 0.05$ (2-factor mixed-model ANOVA).

$^5$ Significant difference between normal-weight, overweight, and obese subjects at baseline, $P < 0.05$ (one-factor ANOVA followed by Bonferroni correction).

$^6$ Significant overfeeding × adiposity status interaction, $P < 0.05$ (2-factor mixed-model ANOVA followed by Bonferroni correction when significant).

$^7$ Significant difference within group, $P < 0.05$ (paired $t$ test).

$^8$ Significant difference between obese and normal-weight and between obese and overweight subjects at baseline, $P < 0.05$ (one-factor ANOVA, followed by Bonferroni correction).
Correlations of PYY with phenotypes of glucose and lipid metabolism

Correlations between baseline PYY and baseline phenotypes were assessed (Table 2). In the entire cohort at baseline, PYY was negatively correlated with BMI. However, when these analyses were repeated according to adiposity status, the correlation was only found in normal-weight and overweight subjects. PYY was not significantly correlated with %BF in the entire cohort, but was found to be negatively correlated with %BF within the normal-weight subjects. Baseline PYY was negatively correlated with baseline %AF within the normal-weight group. Correlations between baseline PYY and the changes in phenotypes were also assessed (Table 4). Three significant negative correlations were found within the normal-weight group between baseline PYY and the changes in total cholesterol, LDL cholesterol, and HDL cholesterol because of overfeeding. Also, baseline PYY was negatively correlated with the changes in glucose in overweight subjects. Correlations between changes in baseline PYY and changes in phenotypes were also assessed (Table 4). Only 2 positive partial correlations were found between the changes in PYY and the changes in phenotype markers as a result of overfeeding: HDL cholesterol and glucose in normal-weight subjects (Table 4).

Comparison of body-composition measures in subjects with low, medium, and high baseline fasting serum PYY concentrations

Last, we investigated the relation between low, medium, and high baseline fasting serum PYY concentrations and markers of...
Glucose 0.101 NS 0.420 0.033
HDL cholesterol 0.204 NS 0.507 0.008
Percentage android fat 0.062 NS 0.164 NS 0.187 NS
Percentage trunk fat 0.155 NS 0.199 NS 0.318 NS 0.159 NS
Percentage body fat 0.141 NS 0.187 NS 0.372 NS 0.148 NS
BMI 0.018 NS 0.186 NS
HOMA-IR 0.069 NS 0.062 NS 0.135 NS 0.221 NS
Insulin 0.068 NS 0.057 NS 0.240 NS 0.019 NS
Weight 0.019 NS 0.187 NS

1 HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function. Partial correlation analysis after control for age was used to screen for the potential changes in factors due to overfeeding related to the potential changes in peptide YY due to overfeeding. Subjects were classified on the basis of percentage body fat as normal weight (8–20.9%), overweight (21–25.9%), or obese (≥26%) according to criteria recommended by Bray (25).
2 Not significant after Bonferroni correction to adjust for multiple variables tested.

body composition. The between-group comparison showed no significant differences in any of the body-composition variables (body weight, BMI, %BF, %TF, and %AF) at baseline or after the overfeeding protocol. The values for %BF at baseline—stratified by low, medium, and high PYY concentrations—were 24.54 ± 8.2%, 22.6 ± 8.9%, and 22.13 ± 8.5%, respectively, and were not significantly different from one another (P = 0.606). BMI at baseline—stratified by low, medium, and high PYY concentrations—were 26.66 ± 4.8, 24.80 ± 4.7, and 25.14 ± 4.4, respectively and were also not significantly different from one another (P = 0.469). The 2-factor ANOVA again showed that the 7-d overfeeding protocol effectively increased whole PYY concentrations (P = 0.002) and showed a significant overfeeding × PYY concentration group interaction (P < 0.001). Subgroup analysis showed that PYY increased significantly within the low baseline PYY group from 61.87 ± 19.43 to 103.51 ± 37.01 pg/mL (P ≤ 0.05), but remained unchanged after overfeeding in the medium (from 114.37 ± 10.30 to 115.18 ± 43.37 pg/mL) and high (from 178.03 ± 50.14 to 194.43 ± 85.72 pg/mL) baseline PYY concentration groups.

DISCUSSION

The gastrointestinal tract is the largest endocrine organ in the human body and secretes several appetite-regulating hormones, including PYY. The brainstem and hypothalamus receive neural and hormonal signals through a gut-brain communication pathway, which subsequently regulate food intake and energy homeostasis (27, 28). Although PYY is thought to be involved in the development of obesity (29), controversy exists regarding the definitive role that PYY plays in this regard (6, 15, 18). Therefore, we sought to clarify whether fasting serum PYY varied before and after a positive energy challenge in normal-weight, overweight, and obese young men.

Data from animal experiments indicate that endogenous PYY acts on the arcuate nuclei through the gut-hypothalamic pathway and blocks various orexigenic effects, which results in increased satiety and decreased gastric emptying (5, 29, 30). It has been suggested that fasting serum PYY concentrations are lower in obese rodents and in humans and that PYY infusion effectively reduces food intake and body weight (5, 29). However, many other studies have failed to reproduce these findings (15, 18). In our study, we found no significant differences in fasting serum PYY concentrations between normal-weight, overweight, or obese men classified by %BF (by DXA) or BMI. Furthermore, no significant differences were observed between body-composition measurements made by DXA or BMI when our subjects were stratified into low, medium, and high fasting serum PYY concentrations. Therefore, our data do not support the hypothesis that adiposity status, indexed by %BF or BMI, determines basal PYY concentrations. Interestingly, we did observe an inverse correlation between circulating PYY and markers of adiposity (%BF and BMI) in normal-weight subjects. Although the reason for this is unclear, it appears that PYY may have a weak effect on adiposity in normal-weight men. Nonetheless, without a number of large population-based studies on fasting serum concentrations of human PYY, strong conclusions regarding the role that PYY plays in determining adiposity status and the development of obesity will remain controversial.

The most important finding from the current study is that the concentration of fasting PYY significantly increased in all subjects after a 7-d overfeeding challenge. In addition, the amount of PYY significantly increased in the low PYY concentration group and not in the medium and high concentration groups, which suggests a possible dose effect. This finding is difficult to interpret without further study. It was first suspected that most of the PYY subjects with a low baseline concentration experienced an increase in PYY in response to the positive energy challenge would have been from the normal-weight group. However, because only 9 of the 23 subjects with a low PYY concentration were of normal weight, we doubt that this possible dose effect would be dependent on adiposity status. In addition, having divided our subjects into groups according to a baseline measurements, it cannot be ignored that the regression to the mean may partially explain both the increase in PYY in the low PYY concentration.
group and the increase in %BF in the normal-weight group after our intervention. Previous studies that investigated the role of PYY in maintaining energy homeostasis have examined the response of this gut hormone to a negative energy balance (6, 17). Specifically, a study by Essah et al. (17) in 30 obese adults showed a 9% reduction in body weight and a subsequent 10% reduction in circulating PYY concentrations after an 8-wk low-fat and low-carbohydrate hypocaloric diet (17). Although the study provides valuable insight into the regulation of PYY by a negative energy challenge, obesity is generally understood to be the result of a chronic energy surplus (31) that triggers many complex hormonal changes (32, 33). The current overfeeding study, therefore, provides a means by which the biochemical changes in circulating PYY that would be evident with extended overeating, such as in the development of obesity, could be examined. The significant increase in PYY in response to a positive energy challenge in our study could be physiologically meaningful and act as a protective mechanism to counteract the hypercaloric diet. However, the increase in PYY due to overfeeding is not dependent on adiposity status, which suggests hope that PYY could potentially be helpful to overweight and obese individuals. Our results, combined with data from previous negative energy balance studies, suggest that PYY is involved in maintaining energy homeostasis; however, the level of contribution is yet to be determined.

Aside from investigating the role PYY plays in body composition and energy homeostasis, we were also interested in investigating its association with variables of glucose and lipid metabolism. Interestingly, baseline PYY was found to be negatively correlated with the increase in cholesterol measurements (total, LDL, and HDL cholesterol) in response to overfeeding in normal-weight subjects. This finding would suggest that individuals with lower baseline PYY concentrations experience a greater increase in serum lipids after overfeeding. Although the parallel response between PYY and serum lipids may be beneficial when under a positive energy balance, a causal relation between these variables cannot be inferred. More studies are warranted to further understand the possible physiological significance between fasting PYY and serum lipids under a positive energy challenge.

The primary limitation of the present study was that we only studied young men (19–29 y of age), which limits the application of our conclusions to other groups. Larger population studies investigating the effects of overfeeding with a wider age distribution including females is warranted to determine the physiologic role that PYY plays in the modification of appetite and the development of obesity. Furthermore, we only investigated whole human PYY rather than PYY3-36, which has been suggested to be the more significantly active form of PYY. However, whole PYY concentrations are positively correlated with PYY3-36 (11), and both PYY3-36 and PYY1-36 have been found to decrease gastrointestinal motility (6).

In summary, this is the first study of its kind to explore the response of fasting PYY to a short-term positive energy challenge. We measured fasting serum whole PYY in 69 young men before and after a 7-d positive energy challenge. Circulating PYY was similar among normal-weight, overweight, and obese young men at baseline before overfeeding. We did, however, observe significant negative correlations with both BMI and %BF in normal-weight subjects only. Furthermore, PYY was significantly increased in response to the positive energy challenge in the entire cohort. It would appear that PYY acts as a protective mechanism against the development of obesity. The body seems to mount a counterregulatory reaction to prevent further weight gain in normal-weight, overweight, and obese subjects. Therefore, PYY represents a likely target for further downstream studies related to the development of obesity.

We greatly appreciate the contributions of the volunteers to the present study. We also recognize the following members who contributed to the data collection: Sammy Khalili, Curtis French, and Jessica Bishop. The authors’ responsibilities were as follows—FC: conducted the data analysis and statistical analysis and wrote the manuscript; JLS: assisted with the manuscript revisions; ER: assisted with the PYY measurement and the manuscript revision; SV: assisted with the insulin measurements and manuscript revision; and GS: designed the study and revised the manuscript. None of the authors had a personal or financial conflict of interest.

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