Physiological Evidence for the Involvement of Peptide YY in the Regulation of Energy Homeostasis in Humans

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Abstract

GUO, YAN, LIJUN MA, PABLO J. ENRIORI, JURAJ KOSKA, PAUL W. FRANKS, THOMAS BROOKSHIRE, MICHAEL A. COWLEY, ARLINE D. SALBE, ANGELO DELPARIGI, AND P. ANTONIO TATARANNI. Physiological evidence for the involvement of peptide YY in the regulation of energy homeostasis in humans. *Obesity.* 2006;14:1562–1570.

Objective: To explore the potential role of the endogenous peptide YY (PYY) in the long-term regulation of body weight and energy homeostasis.

Research Methods and Procedures: Fasting and postprandial plasma PYY concentrations were measured after an overnight fast and 30 to 180 minutes after a standardized meal in 29 (21 men/8 women) non-diabetic subjects, 16 of whom had a follow-up visit 10.8 ± 1.4 months later. Ratings of hunger and satiety were collected using visual analog scales. Resting metabolic rate (RMR) (15-hour RMR) and respiratory quotient (RQ) were assessed using a respiratory chamber.

Results: Fasting PYY concentrations were negatively correlated with various markers of adiposity and negatively associated with 15-hour RMR ($r = -0.46$, $p = 0.01$). Postprandial changes in PYY (area under the curve) were positively associated with postprandial changes in ratings of satiety ($r = 0.47$, $p = 0.01$). The maximal PYY concentrations achieved after the meal (peak PYY) were negatively associated with 24-hour RQ ($r = -0.41$, $p = 0.03$). Prospectively, the peak PYY concentrations were negatively associated with changes in body weight ($r = -0.58$, $p = 0.01$).

Discussion: Our data indicate that the endogenous PYY may be involved in the long-term regulation of body weight. It seems that this long-term effect was not exclusively driven by the modulation of food intake but also by the control of energy expenditure and lipid metabolism.

Key words: peptide YY, body weight, energy homeostasis

Introduction

The gut hormone peptide YY (PYY)[1] belongs to a family of peptides that includes pancreatic polypeptide and neuropeptide Y (NPY). It is secreted by the L cells of the lower intestine after meal ingestion and released into the circulation (1), where it exists in two endogenous forms: $PYY_{1–36}$ and $PYY_{3–36}$ (2). $PYY_{1–36}$ is the major form of PYY in the fasting state (2). The latter form is produced by the action of the enzyme dipeptidyl peptidase-IV in response to food intake (3).

Peripheral administration of $PYY_{1–36}$ reportedly decreases food intake in rodents (4). $PYY_{3–36}$ also markedly inhibits food intake in rodents (5,6) and has been shown to cross the blood-brain barrier and act on the arcuate nucleus of the hypothalamus (6,7) with a high affinity for the Y2

Received for review July 12, 2005.

Accepted in final form June 19, 2006.

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[1] Nonstandard abbreviations: PYY, peptide YY; NPY, neuropeptide Y; Y2R, Y2 receptor; EE, energy expenditure; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; OGTT, oral glucose tolerance test; RMR, resting metabolic rate; $V\text{CO}_2$, carbon dioxide production; $V\text{O}_2$, oxygen consumption; RQ, respiratory quotient; AUC, area under the curve; GGT, γ-glutamyltranspeptidase.

receptor (Y2R) (5,8). Animal studies have shown that $PYY_{3–36}$ inhibits hypothalamic NPY expression by binding to Y2R (5); mice lacking the Y2R gene have increased body weight, food intake, and fat deposition (9). Contrary to these findings, Tschöp et al. (10) have recently reported no effect of peripherally administered PYY in rodents. The reasons for this discrepancy remain unclear. However, a study in non-human primates demonstrated that acute administration of $PYY_{3–36}$ reduces daily food intake in rhesus monkeys by increasing the latency of initiation of daily feeding and decreasing the subsequent meal size, although repeated administration across days did not maintain the decrease in food intake (11).

Batterham et al. (12) first demonstrated that $PYY_{3–36}$ affected eating behavior in human subjects. Exogenous administration of physiological doses of PYY reduced appetite and food consumption by ~30% compared with saline infusion. Moreover, fasting plasma PYY concentrations were lower in obese as compared with lean subjects (12). However, the PYY data related to human appetite and food intake have been limited to the report of the acute effect of a single infusion. Although others (13) reported that the exaggerated postprandial PYY may contribute to satiety and the ability to reduce meal size and body weight after gastric bypass surgery, whether PYY is also effective as a long-term modulator of body weight in humans remains to be investigated. Furthermore, little is known about the role of physiological/endogenous PYY in the regulation of energy homeostasis in humans. The purpose of our study was to use prospective analyses to establish whether circulating concentrations of PYY are associated with changes in body weight in non-diabetic adults. We also sought to explore whether PYY regulates body weight homeostasis in humans by affecting energy intake, energy expenditure (EE), or both. We hypothesized that higher concentrations of the fasting and postprandial PYY would be associated with a lower risk of weight gain primarily because of its anorectic effect.

Research Methods and Procedures

Twenty-nine subjects (21 men/8 women) were admitted to the metabolic ward of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for 6 to 10 days. All subjects were free from any other diseases, except 13 subjects were obese. None of the subjects was taking medications or smoking cigarettes, or had a history of eating disorders. Women were in the follicular phase of the menstrual cycle during the time they were studied. On admission, all subjects were fed a weight-maintaining diet (50%, 30%, and 20% of daily calories provided as carbohydrate, fat, and protein, respectively) calculated on the basis of body weight. Percentage of body fat was estimated by DXA (14). At the follow-up visit (10.8 ± 1.4 months), 16 (13 men/3 women) of the 29 subjects had their height and weight remeasured and underwent an oral glucose tolerance test (OGTT). Subjects who developed any diseases at follow-up were excluded. The protocol was approved by the institutional review board of the NIDDK and the Indian Health Service. All subjects gave written, informed consent before participation.

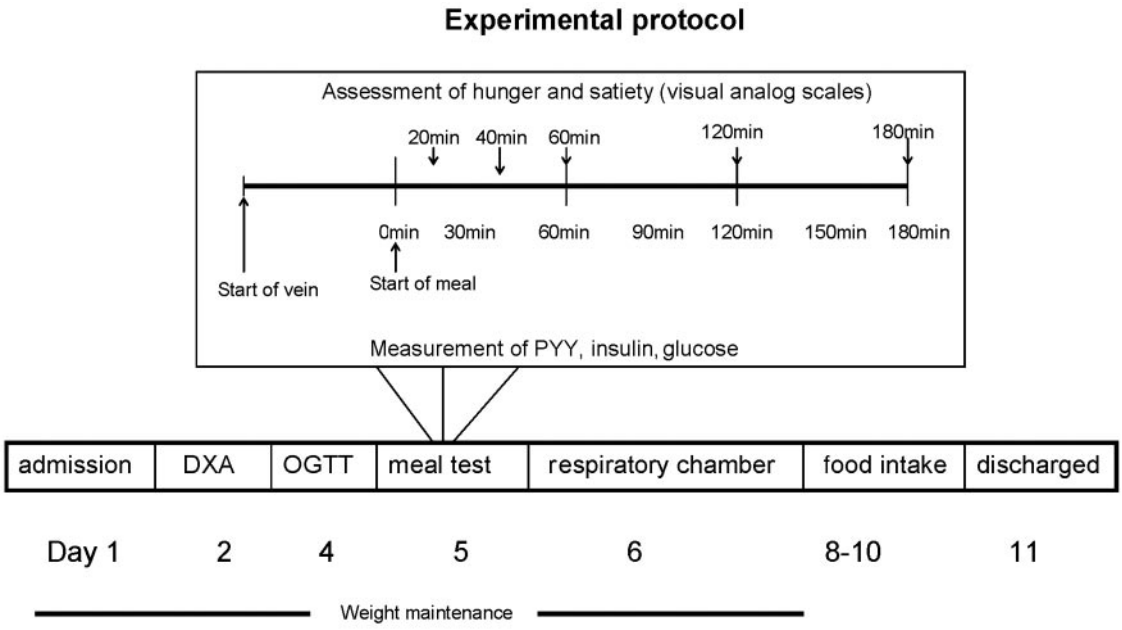

Figure 1: Graphically illustrated experimental protocol.

The experimental protocol is graphically illustrated in Figure 1. At least 3 days after admission, subjects underwent an OGTT after an overnight fast. The following day, after fasting for 12 hours, subjects underwent a meal test. An intravenous catheter was placed in an antecubital vein for blood sampling and kept patent with a 0.9% saline infusion. At ~8:30 AM, subjects were fed a standardized meal calculated on the basis of body weight (15) (bacon and egg sandwich, percentage of calories: protein, 10%; fat, 45%; carbohydrates, 45%; providing 20% of daily energy requirements), and all subjects consumed the meal within 15 minutes and rested quietly in bed throughout the study. Subjective feelings of hunger and satiety were assessed by visual analog scale every 20 minutes for the 1st hour and then hourly for 2 hours.

Blood samples were drawn into pre-chilled syringes before and after administration of the meal and at 30-minute intervals for 3 hours. An aprotinin (dipeptidyl peptidase-IV) inhibitor was added to the syringes to prevent the degradation of PYY. The measurement of PYY was accompanied by simultaneous measures of glucose and insulin concentrations. Plasma PYY concentration was assayed by radioimmunoassay. All samples were assayed in duplicate. PYY immunoreactivity was measured with a specific and sensitive radioimmunoassay that detected both the cleaved form ($PYY_{3–36}$) and the full-length hormone ($PYY_{1–36}$). The antibody cross-reacts fully with the biologically active circulating forms of human PYY, but not with pancreatic polypeptide, NPY, or other known gastrointestinal hormones (Bachem, Bubendorf, Switzerland). The intra-assay variation (coefficient of variation) was determined by replicate analysis ($n = 12$) of two samples at PYY concentrations of 50 and 200 pg/mL, and the results were 7.7% and 6.7%, respectively. The inter-assay variations (coefficients of variation) were 8.2% and 7.5% for the range of values measured. The lowest detectable level that could be distinguished from the zero standard was 8.4 pg/mL. Glucose concentrations were determined by the glucose oxidase method (Beckman Instruments, Fullerton, CA), and plasma insulin concentrations were determined by automated radioimmunoassay (ICN Biochemicals, Costa Mesa, CA).

On the day after the meal test, subjects spent 23 hours in a respiratory chamber for the measurement of EE and substrate oxidation, as previously described (16). In brief, volunteers entered the chamber at 7:45 AM after an overnight fast and remained therein for 23 hours. Meals were provided at 8 AM, 11:30 AM, 4 PM, and 7 PM. Vigorous exercise was not permitted. The rate of EE was measured continuously, calculated for each 15-minute interval, and then extrapolated to 24 hours (24-hour EE). Mean resting metabolic rate (RMR) was obtained between 8 AM and 11 PM (15-hour RMR), calculated from the intercept of the linear regression between EE and spontaneous physical activity measured by radar (17). Carbon dioxide production (V_{CO_2}) and oxygen consumption (V_{O_2}) were calculated for each 15-minute interval and then extrapolated to 24 hours. The 24-hour respiratory quotient (RQ) was calculated as the ratio of 24-hour V_{CO_2} and 24-hour V_{O_2}. The substrate balances were calculated as previously described (16).

Twenty (12 men/8 women) of the 29 subjects completed an ad libitum food intake study during the same admission. Subjects were asked to self-select all their food using a computer-operated vending machine system for 3 consecutive days (18). The 40 food items made available to the subjects on each of the 3 days consisted of those foods to which the subject had assigned an intermediate hedonic rating on a food preferences questionnaire. Subjects had ad libitum access to the vending machines for 23.5 hours/d. The refrigerated machines were housed in a separate eating area equipped with a table, chair, microwave oven, and toaster. Subjects were instructed to eat only in the vending room and to eat whatever they wished whenever they desired. Television viewing during food consumption was prohibited. Food wrappers and unconsumed food portions were returned to the vending machines.

Daily energy, protein, fat, and carbohydrate intakes were calculated from the actual weights of food and condiments consumed using the CBORD Professional Diet Analyzer Program (CBORD, Inc., Ithaca, NY) with the database modified to reflect the nutrient content of specific food items as indicated by the manufacturer.

Statistical Analyses

Data were analyzed by using the software of the SAS Institute (Cary, NC). Results are presented as means ± standard error. Postprandial changes in PYY, insulin, and glucose concentrations and changes in hunger and satiety ratings are expressed as the area under the curve (AUC) calculated above the baseline by the trapezoid method. The maximal concentration of PYY achieved after the meal is expressed as the peak PYY. Food intake variables were calculated as the average of 3-day total food and fat consumption and are presented as mean 24-hour calorie intake and mean fat intake.

The relationships between fasting PYY concentrations and selected anthropometric and metabolic variables in the cross-sectional analyses were examined by calculating Spearman correlation coefficients. RMR and/or RQ were further adjusted for age, sex, and body composition or age, sex, percentage of fat, and energy balance, respectively, using linear regression models before the correlation analyses (16,19). One-way ANOVA (PYY on ranks) was used to determine the statistical significance of changes in the variables after meal ingestion.

General linear regression models were used to evaluate the effect of PYY concentrations on body weight at follow-up adjusted for baseline body weight, age, sex, and time

Table 1. Anthropometric and metabolic measurements at baseline and follow-up

	Cross-sectional ($N = 29$)	Prospective (baseline) ($N = 16$)	Prospective (follow-up) ($N = 16$)
Age (years)	31 ± 1.4 (18.7 to ~45.8)	29 ± 1.7	30 ± 1.7
Body weight (kg)	88 ± 3 (59 to ~120)	93 ± 4	92 ± 5
BMI (kg/m^2)	30 ± 1.3 (19.7 to ~45.5)	32 ± 1.6	31 ± 1.7
Body fat (%)	28 ± 2 (7.6 to ~46.5)	31 ± 2	28 ± 3
Waist circumference (cm)	102 ± 3 (74 to ~138)	106 ± 3	104 ± 3
Fasting plasma glucose (mg/dL)	87 ± 1.3	89 ± 1.6	88 ± 1.7
2-hour glucose OGTT (mg/dL)	117 ± 4.7	120 ± 5.7	113 ± 7.7
Fasting plasma insulin ($\log_{10}$, mU/L)	1.47 ± 0.02	1.50 ± 0.03	
Fasting triglyceride (mg/dL)	138 ± 13	133 ± 13	
Fasting GGT (U/L)	41 ± 4.7	52 ± 6.8	
Fasting PYY (pg/mL)	60 ± 7.9	49 ± 5	
Postprandial PYY_{AUC}	3274 ± 1373	3407 ± 1142	
Postprandial peak PYY (pg/mL)	121 ± 8	104 ± 7	
Postprandial satiety, VAS_{AUC}	5232 ± 1078	4848 ± 1513	
24-hour EE (kcal)	2378 ± 66	2446 ± 80	
24-hour RQ ($V\mathrm{CO}_2/V\mathrm{O}_2$)	0.84 ± 0.00	0.84 ± 0.00	
15-hour RMR (kcal/d)	2162 ± 60	2217 ± 68	
24-hour energy intake (kcal/d)	4176 ± 287	4377 ± 400	
24-hour fat intake (grams/d)	182 ± 14	198 ± 20	

OGTT, oral glucose tolerance test; GGT, γ-glutamyltranspeptidase; PYY, peptide YY; VAS_{AUC}, the area under the visual analog scale curve; EE, energy expenditure; RQ, respiratory quotient; $V\mathrm{CO}_2$, carbon dioxide production; $V\mathrm{O}_2$, oxygen consumption; RMR, resting metabolic rate.
Results are means ± SE.

of follow-up. To fit this model, PYY concentrations were standardized by calculating z scores (mean, 0; standard deviation, 1).

Results

The anthropometric and metabolic characteristics of the study population and of the subgroup of subjects who had a follow-up visit are summarized in Table 1. In cross-sectional analyses, fasting PYY concentrations were inversely correlated with various measurements of adiposity including BMI, percentage of body fat, and waist circumference, although not all of the relationships reached a formal level of statistical significance ($p = 0.05$) (Table 2). No associations were found between fasting PYY concentrations and age or fasting glucose and insulin concentrations. We found a negative correlation between fasting PYY and fasting triglyceride concentrations and with fasting γ-glutamyltranspeptidase (GGT) concentrations both before and after adjustment for percentage of body fat (Table 2). Fasting PYY concentrations were also negatively correlated with 15-hour RMR before and after adjustment for age, sex, and body composition (Table 2; Figure 2).

Meal-induced changes in plasma concentrations of PYY, glucose, and insulin and changes in subjective ratings of hunger and satiety are shown in Figure 3. After the meal, PYY, insulin, and glucose concentrations significantly increased ($p < 0.001$). The subjective ratings of satiety also increased, whereas the subjective ratings of hunger decreased ($p < 0.001$). The peak PYY concentration occurred much later than that of insulin and glucose (Figure 3).

Postprandial changes of PYY (AUC) were positively associated with the changes in the subjective ratings of self-reported satiety (Table 2). Peak PYY concentrations were negatively correlated with 24-hour RQ after adjusting for age, sex, percentage of body fat, and energy balance (Table 2 and Figure 2). Neither fasting PYY concentrations nor the postprandial PYY responses (AUC or peak) were associated with either mean 24-hour total calorie intake or mean fat intake adjusted for body weight (Table 2).

Fasting PYY concentrations were not associated with follow-up changes in body weight. Postprandial peak PYY

Table 2. Spearman correlation coefficients between PYY levels and anthropometric and metabolic variables

	Fasting PYY	Postprandial PYY AUC	Postprandial PYY peak
Age	0.21	−0.25	−0.04
Weight	−0.26	0.16	−0.34
BMI	−0.41*	0.31	−0.32
Body fat	−0.35	0.23	−0.27
Waist circumference	−0.39*	0.28	−0.35
Fasting triglyceride	−0.42*	0.22	−0.23
Fasting GGT	−0.47*	0.27	−0.34
Fasting insulin	−0.17	−0.04	−0.41*
Postprandial insulin, AUC	−0.44*	0.13	−0.15
Fasting glucose	0.00	−0.12	−0.17
Postprandial glucose, AUC	−0.25	0.11	−0.3
Satiety, AUC	−0.25	0.47*	0.23
Hunger, AUC	0.08	−0.24	−0.04
24-hour energy intake	−0.09	0.06	−0.19
24-hour fat intake	−0.01	−0.08	−0.26
24-hour EE	−0.31	0.16	−0.21
15-hour RMR	−0.46*	0.22	−0.02
24-hour RQ	0.24	−0.34	−0.41*

PYY, peptide YY; AUC, area under the curve; GGT, γ-glutamyltranspeptidase; EE, energy expenditure; RMR, resting metabolic rate; RQ, respiratory quotient.
AUC represent the overall change after meal ingestion. Fifteen-hour RMR adjusted for age, sex, fat mass, and fat free mass. Twenty-four-hour RQ adjusted for age, sex, percentage of fat, and energy balance.
* $p < 0.05$.

concentrations were negatively correlated with changes in body weight (range, 15.8 to approximately ~+9.5 kg) in a general linear regression model where weight at follow-up was adjusted for sex, baseline age and body weight, and the time of follow-up (Figure 4). Postprandial peak PYY concentrations were also a significant determinant of changes in waist circumference over time (data not shown).

Discussion

In the present study, we tested the hypothesis that higher fasting and postprandial PYY concentrations were associated with a lower risk of weight gain primarily because of its anorectic effect. Although we did find that the postprandial increase in PYY concentrations was associated with increased self-reported feelings of satiety, and the high postprandial peak PYY concentrations were prospectively associated with a low risk of weight gain, we did not observe any associations between PYY and ad libitum food intake. However, we found that a high fasting and postprandial peak PYY concentrations were associated with a low RMR and a low RQ, respectively, two recognized metabolic predictors of weight change in humans (19–22).

Body weight homeostasis is maintained by the balance between energy intake and EE. Appetite is one of the factors that affect energy intake. It has been suggested recently that the gut hormone PYY suppresses appetite not only by the ileal brake mechanism (the slowing of gastrointestinal motility after nutrient ingestion causes the sensation of satiety) (23,24) but may also be a modulator of central satiety signal (5). In the present study, the time course of the changes in satiety and PYY concentrations after a meal were not synchronous, but, on average, the magnitude of the satiety and PYY responses as assessed by the AUC were proportional. Although this observation does not establish causality, this finding is, therefore, in line with the evidence suggesting that PYY may be a satiety hormone. Several pathways have been proposed for the anorexigenic effect of PYY. It may act on presynaptic Y2R to reduce an orexigenic drive on NPY neurons and to stimulate adjacent anorexigenic pro-opiomelanocortin neurons (5). PYY may also directly inhibit the orexigenic effects of ghrelin-activated neurons in the arcuate nucleus (25).

The acute effects of elevated circulating PYY concentrations on satiety have been experimentally proven in infusion

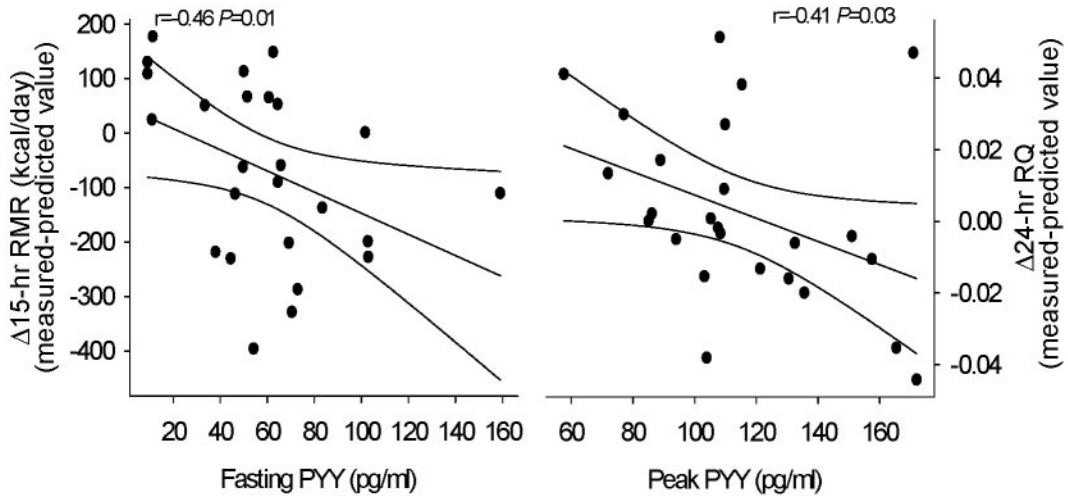

Figure 2: The cross-sectional relationship between fasting PYY concentrations and RMR after adjustment for age, sex, fat mass, and fat free mass (left); the relationship between postprandial peak PYY concentrations and RQ after adjustment for age, sex, percentage body fat, and energy balance (right) in 29 non-diabetic subjects.

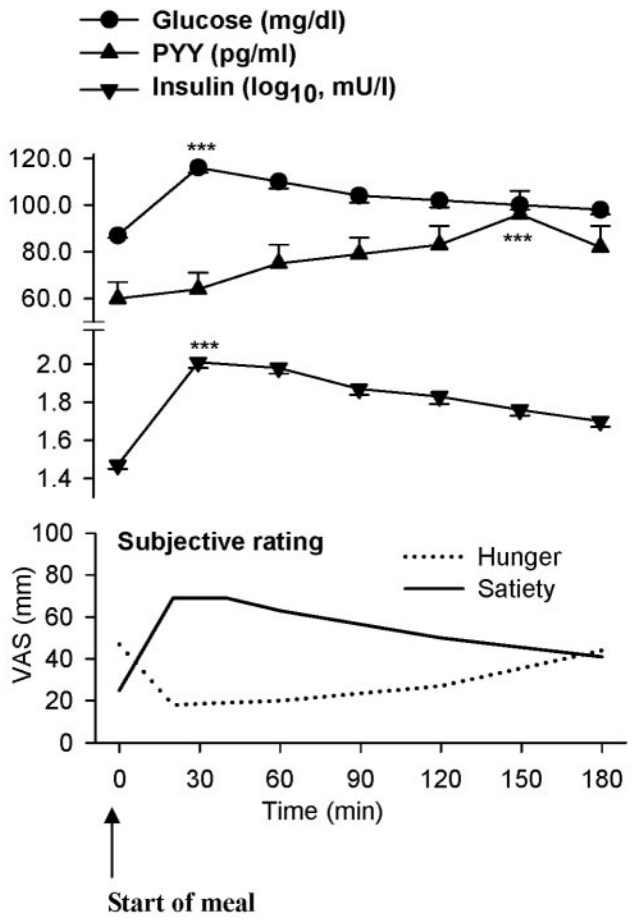

Figure 3: Postprandial curves (mean ± standard error) of PYY, glucose, insulin and subjective ratings of hunger, and satiety in 29 subjects. *** Average peak.

experiments and bypass surgery (12,13) but cannot provide any evidence that PYY is involved in the long-term regulation of body weight. Our study and others (12) have shown that circulating concentrations of PYY are low in obese individuals, suggesting a possible etiologic/pathophysiological role and a potential therapeutic opportunity. It is plausible for PYY to have long-term effect on energy homeostasis because postprandial release of PYY may last for a longer period of several hours. Thus, it has been termed an intermediate signal (26). Unlike short-term satiety hormone cholecystokinin (27), PYY may not only decrease meal size but also meal frequency (11), the reduction of meal size is not compensated by the initiation of more frequent meal events; therefore, body weight is prone to decrease. Another possibility is that PYY stimulates the synthesis and secretion of apolipoprotein A-IV by the gastrointestinal tract, which may also be involved in long-term regulation of food intake and body weight (28,29). Data from experimental animals on the involvement of PYY in the long-term regulation of body weight have yielded conflicting results. Batterham et al. (5) reported that intraperitoneal application of $PYY_{3–36}$ to rats for 1 week produced a sustained decrease in body weight. Pittner et al. (30) demonstrated that a 4-week infusion of PYY reduced weight gain in female *ob/ob* mice, without affecting the cumulative food intake. In contrast, studies from 12 laboratories have failed to show the weight reducing effect of intraperitoneally administered $PYY_{3–36}$ in rodents (10). Human interventional studies have thus far been limited to the effect of an acutely administered single dose of PYY and cannot yet answer the question as to whether the acute effects of PYY on energy balance are sustained over repeated administrations and whether this is the role of endogenously produced PYY.

Our prospective analyses provide the first evidence that the endogenous PYY may be involved in the long-term regulation of body weight in humans because our data showed the postprandial peak PYY concentrations were associated with the follow-up changes of body weight. However, fasting PYY was not a determinant of weight change in the same group of people leading some to argue about the inconsistency of these findings. This might be due to the limitation of our assay that cannot identify the two forms of the circulating PYY separately. Grandt et al. (2) have reported that the percentage of the two forms of PYY in human blood differs according to feeding status. In the fasted state, the concentration of $PYY_{1–36}$ predominates over that of $PYY_{3–36}$. In contrast, after a meal, $PYY_{3–36}$ is the major circulating form. It has also been reported that $PYY_{3–36}$ is more potent than $PYY_{1–36}$ in suppressing food intake in rats (31); thus, fasting and postprandial peak PYY may have different efficacy on food intake. However, in a further examination of the role of the fasting and the postprandial peak PYY on food intake using the vending machine system, we did not find any evidence that they were related to ad libitum food consumption; thus, we are unable to conclude from our study that the effect of the postprandial peak PYY on body weight change was primarily driven by the modulation of food intake.

In addition to energy intake, EE and fat oxidation/synthesis are also mechanisms through which body weight is regulated. To our knowledge, no studies have previously explored the possible role of PYY in the control of EE. Fasting PYY concentrations in our study were negatively associated with RMR, which is the largest portion of total daily EE (60% to 75%). Because the major form of fasting PYY is $PYY_{1–36}$, which binds to and activates at least three NPY receptors (Y1, Y2, and Y5) (32), although activation of Y1 or Y2 receptors has not been reported to affect EE, activation of Y5 receptor has been found to decrease EE in rodents (33). However, whether fasting PYY can decrease EE by binding to Y5 receptor in humans is beyond the investigation of our study. Our results at least suggest that fasting PYY might be involved in the control of EE.

Importantly, our study demonstrated that a high postprandial peak PYY was cross-sectionally associated with a low RQ. This finding was consistent with our prospective analysis that the high postprandial peak PYY concentrations were associated with a low risk of weight gain because a low RQ indicates a relatively high level of fat oxidation and has been identified as a protective against weight gain in different populations (19,21). It has long been recognized that the microinjection of NPY into the paraventricular nucleus of the hypothalamus stimulates eating and increases RQ (34). As we know, the major form of the postprandial peak PYY is $PYY_{3–36}$, which may selectively act on the Y2R to inhibit the release of NPY. This is the possible pathway that postprandial peak PYY stimulates lipid oxidation; it is, therefore, possible that PYY regulates body weight homeostasis by participating in the regulation of whole-body lipid metabolism. It is tempting to speculate that the low concentrations of triglyceride and GGT (a marker of hepatic steatosis) observed in our study in association with elevated circulating PYY concentrations further supports the role of PYY in lipid metabolism. However, this possibility is weakened by the fact that the associations we found were between fasting PYY concentrations and triglyceride/GGT concentrations, not with postprandial peak PYY concentrations.

There are some limitations in our study. One is that the standardized meal we were choosing was calculated on the basis of body weight, although this approach may have some benefits; for example, the real scale of the subjective ratings of satiety is not biased by the amount of food

Dependent: weight at follow-up R^2=0.95			
Independent	β	S.E.	*P*
Age at baseline	0.85	3.58	0.41
Sex	-0.89	3.77	0.39
Weight at baseline	9.74	0.1	<.0001
Age at follow-up	-0.88	3.76	0.4
Standardized peak PYY (Z-scores)	-2.89	1.46	0.01

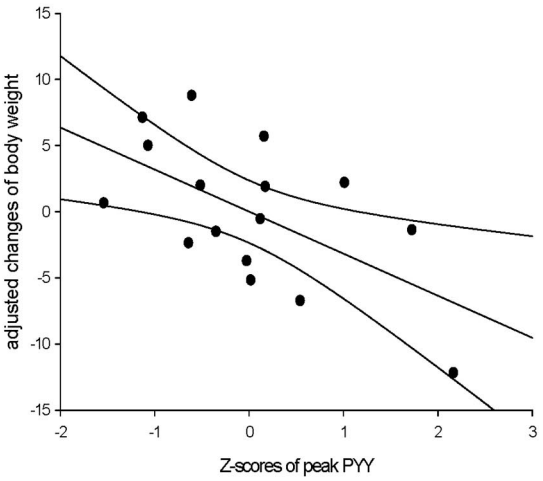

Figure 4: Multivariate relationship between postprandial peak PYY concentrations and changes in body weight in 16 non-diabetic subjects.

digested, and it may still increase the variability of the PYY levels among individuals. The other limitation is that the high drop-out rate in the follow-up study has made it difficult to exclude the possibility of type 1 error in our prospective analysis.

In summary, our data indicate that the endogenous PYY may be involved in the long-term regulation of body weight. It seems this effect is not exclusively achieved by affecting energy intake, but there is evidence that PYY may have some effects on EE and lipid metabolism. Further studies with a larger group of people are needed to confirm the role of this gut hormone in the regulation of energy homeostasis under physiological condition.

Acknowledgments

We acknowledge the nursing and kitchen staff for their care of the patients and the technical staff for assisting with the laboratory analyses. We thank the volunteers for continuing cooperation with the study. We also thank Susan Luther for administrative assistance. This research was supported, in part, by the Intramural Research Program of the NIH, National Institute of Diabetes and Digestive and Kidney Diseases.

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