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Total peptide YY is a correlate of postprandial energy expenditure but not of appetite or energy intake in healthy women

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Abstract

Peptide YY (PYY) and ghrelin have been associated with the regulation of energy balance. The objectives of this study were to determine whether total ghrelin and PYY after a standardized meal predict appetite scores and ad libitum energy intake (EI) and to examine the relationship between total ghrelin and PYY and postprandial energy expenditure (PEE). Twenty-five premenopausal women (age, 50.4 ± 2.0 years; body mass index, 23.5 ± 2.2 kg/m^2) were studied. Total PYY, total ghrelin (enzyme-linked immunosorbent assay), EE (indirect calorimetry), and appetite scores (visual analogue scales) were measured fasting and every 30 minute for 3 hours after the ingestion of a standardized breakfast. Ad libitum EI was measured at lunch with a buffet-type meal. Peptide YY increased ($P < .001$) and total ghrelin decreased ($P < .001$) after breakfast. Significant changes in EE ($P < .001$) and appetite scores ($P < .001$) were noted postprandially. Appetite scores were consistently associated with ad libitum EI at lunch ($r = -0.51$ to 0.40, $P < .05$), whereas no association between EI and prelunch total ghrelin and PYY was observed. Finally, partial correlation analyses revealed that total PYY was a significant independent correlate of PEE at 60, 90, 120, and 150 minutes ($r = 0.37$-0.51, $P \leq .05$). These findings provide evidence that appetite scores are better correlates of EI than are circulating levels of total PYY or ghrelin and that total PYY could be involved in the regulation of PEE.

1. Introduction

Gastrointestinal peptides seem to play an important role in the regulation of feeding [1]. Among these peptides, peptide YY (PYY), first isolated from colonic extracts [2], has been repeatedly shown to increase in the postprandial period [3-6], an increase that has been shown to be proportional to the amount of ingested dietary energy [7], but more so on protein intake [8]. Peptide YY 3-36 also produces a reduction in food intake when administered peripherally [9-12], but pharmacologic plasma levels are seemingly required to obtain this effect in the latter [10]. Ghrelin, a ligand for the growth-hormone secretagogue receptor, is an orexigenic peptide that is predominantly secreted by the oxycintic gland of the stomach [13]. It has been shown that the preprandial rise in ghrelin might serve as a meal initiation signal [14]. Accordingly, intravenous administration of ghrelin increases appetite and food intake [15], whereas the infusion of glucose into the stomach [16] and the ingestion of a meal [17] seem to decrease its levels, although this suppression is less apparent in obesity [18].

Ghrelin and PYY have also been shown to be associated with energy metabolism and substrate partitioning. In animals, ghrelin infusion has been shown to increase respiratory exchange ratio (RER) [19], whereas PYY 3-36 decreases it [20,21]. In human subjects, fasting total ghrelin has been shown to be positively associated to RER [22]. Infusion of PYY 3-36 to humans increases energy expenditure (EE) and fat oxidation [12]. A recent study by Guo and colleagues [23] also reported PYY to be a negative correlate of EE and RER.

To our knowledge, no study has yet investigated the association between total ghrelin and PYY and ad libitum

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feeding and postprandial EE (PEE). The objectives of this study were (1) to determine whether total ghrelin and PYY after a standardized meal predict appetite scores and ad libitum food intake during a buffet-type meal and (2) to examine the relationship between total ghrelin and PYY and PEE.

2. Methods

2.1. Subjects

Twenty-five healthy (body mass index [BMI] = 23.5 ± 2.2 kg/m^2) premenopausal women (age = 50.4 ± 2.0 years) were randomly selected from a larger cohort of 103 women who are part of an ongoing longitudinal study. The inclusion criteria were the following: (1) premenopausal women (*premenopausal status* was defined with the following criteria: [*a*] 2 menses in the 3 months preceding testing, [*b*] no increase in cycle irregularity in the 12 months preceding testing, and [*c*] a follicle-stimulating hormone level less than 30 IU/L); (2) no surgically induced menopause; (3) nonsmoking; and (4) BMI between 20 and 29 kg/m^2. Women were excluded if they (1) were pregnant or planned to become pregnant; (2) had medical problems that could have interfered with outcome variables including cardiovascular and/or metabolic diseases; (3) were taking oral contraceptives, estrogen, or hormone replacement therapy; (4) had high risk for hysterectomy; and (5) had a history of drug and/or alcohol abuse. Informed consent was received from each subject before beginning the study, and the study was approved by both the University of Ottawa and Montfort Hospital research ethics boards.

2.2. Experimental session and measurements

Subjects came to the laboratory on 2 different occasions. During the first visit, body composition, height, and weight were measured. During the second visit, subjects arrived at the laboratory at 7:30 AM; and adherence to preexperimental guidelines was ascertained (12-hour overnight fast and no intense physical activity or alcohol intake for at least 24 hours before testing). A catheter was then inserted into an antecubital vein, and blood was sampled fasting and for 3 hours after the ingestion of a test meal. Appetite scores (visual analogue scale [VAS]) were measured at the same interval as blood sampling. Resting EE (REE) was performed before the ingestion of a standardized breakfast, whereas PEE was evaluated for 3 hours into the postprandial period. The experimental session was then completed by the measurement of energy intake (EI) and macronutrient composition during a buffet-type meal.

2.3. Anthropometry

Height and body weight were measured (HR-100 Height Rod and BWB-800AS Digital Scale from Tanita, Arlington Heights, IL). Body composition was assessed by dual-energy x-ray absorptiometry using a GE-LUNAR Prodigy module (GE Medical Systems, Madison, WI). Coefficient of variation and correlation for the dual-energy x-ray absorptiometry were 1.8% and R = 0.99 as determined in 12 healthy subjects.

2.4. Resting and postprandial energy expenditure and thermic effect of food

Energy expenditure was measured by indirect calorimetry (Deltatrac II metabolic cart; SensorMedics, Yorba Linda, CA). Resting EE was measured for 30 minutes after a 12-hour overnight fast. The first 5 minutes and last 5 minutes were excluded from the calculations; thus, minutes 6 to 25 were used. For PEE, 15-minute sampling periods were performed every 30 minutes for 3 hours into the postprandial period. A mean value (in kilocalories per minute) for each of the 6 PEE measurements was calculated. The thermic effect of food (TEF) was obtained by subtracting REE from PEE for each of the mean values obtained for the 6 sampling periods. Total PEE and TEF were calculated by multiplying the mean value of each of the 6 sampling periods by 30 minutes. These 6 values were then added together to obtain PEE and TEF for the 180-minute period. Energy expenditure was calculated according to the Weir equation [24]. Coefficient of variation and correlation for the determination of REE with the Deltatrac II metabolic cart in our laboratory were 2.3% and R = 0.98, respectively, as determined in 12 healthy subjects. Twenty-four subjects completed the PEE measurements.

2.5. EI and appetite

The standardized breakfast test meal consisted of 2 slices of whole wheat bread (80 g), peanut butter (20 g), strawberry jam (20 g), cheddar cheese 27% milk fat (20 g), and orange juice (250 mL). The total energy content was 575 kcal (2400 kJ), and its food quotient was 0.89 (57% carbohydrates, 13% protein, 30% lipids). Subjects were instructed to eat everything within a 20-minute period (all finished within 10 minutes). Because the response of important study variables (namely, PYY, ghrelin, appetite scores, and PEE) has been shown to be proportional to caloric intake and because this study is cross-sectional, we decided to fix caloric intake at the same level for every subject to reduce interindividual variability. Desire to eat, hunger, fullness, and prospective food consumption (PFC) were rated on a 150-mm VAS that was adapted from Hill and Blundell [25] and is routinely used in our laboratory [22,26]. Energy intake was measured during an ad libitum buffet-type meal offered to subjects at lunch time (3 hours after the standardized breakfast as routinely performed in our laboratory) [26,27].

2.6. Blood sampling, and total PYY and ghrelin assays

As mentioned previously, an intravenous catheter was introduced into an antecubital vein of the nondominant

arm and kept patent with 0.9% NaCl saline drip for further blood sampling. All samples were drawn into tubes containing EDTA. Blood samples were then centrifuged at 3500 rpm at 4°C immediately after each session. Samples were finally stored at −80°C until assayed. Total PYY (includes both PYY 1-36 and 3-36) and total ghrelin (includes both acyl and desacyl ghrelin) were assayed in duplicates with commercially available enzyme-linked immunosorbent assay (PYY and Ghrelin ELISA Kit; Diagnostic Systems Laboratories, Webster, TX). The detection ranges for total PYY and total ghrelin as per manufacturer specifications are from 6 to 2000 pg/mL and 6 to 600 pg/mL, respectively. In our laboratory, intrakit coefficients of variation for PYY and ghrelin were 5.2% and 7.1%, respectively. Interkit variations for these same peptides were 5.8% and 12.0%, respectively. Despite the low interkit variability, it is important to note that all 7 samples for every subject were assayed in the same kit. Values were out of the detection range for 1 of the 25 subjects for total ghrelin and for 1 of the 25 subjects for PYY. Thus, 24 subjects were included in the analyses for these 2 peptides.

2.7. Statistics

All statistical analyses were performed using Statistical Product and Service Solutions software, version 15.0 (SPSS, Chicago, IL). A 1-way repeated-measures analysis of variance with 1 within factor (time) was used to assess the effects of the standardized breakfast on VAS, EE, and peptides. Pearson correlation analyses were performed between peptides and appetite and EI measurements as well as between peptides and EE measurements. Finally, partial correlation analyses controlling for body weight were performed between PYY and EE measurements. Effects were considered significant at $P \leq .05$, and data are presented as mean ± SD.

3. Results

Subjects' characteristics are presented in Table 1. The premenopausal women (50.4 ± 2.0 years) had a normal body weight (61.7 ± 5.7 kg) and were nonobese (23.5 ± 2.2 kg/m^2).

Table 1
Subjects' characteristics

Variables	Mean	Range
Age (y)	50.4 ± 2.0	47-55
Weight (kg)	61.7 ± 5.7*	53.0-72.7
Height (cm)	162.2 ± 7.8	151-181
BMI (kg/m^2)	23.5 ± 2.2	19.6-28.4
Fat mass (kg)	19.7 ± 4.8	11.4-28.5
Fat-free mass (kg)	39.1 ± 3.7	34.2-47.3
Body fat (%)	32.0 ± 6.1	21.2-41.7

Values are means ± SD. N = 25.
* Body weight was measured with the digital scale and not the DXA.

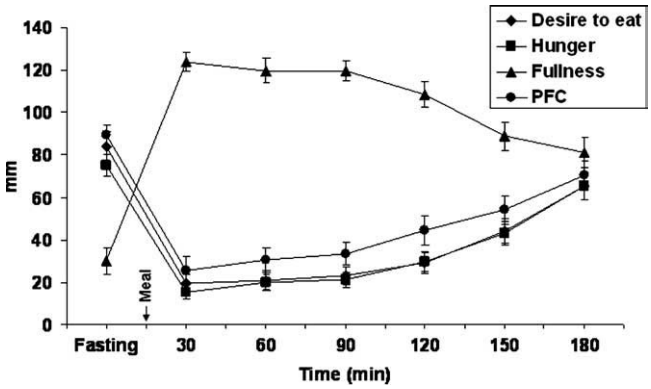

Fig. 1. Desire to eat (◆), hunger (■), fullness (▲), and PFC (●) fasting and for 3 hours after a standardized breakfast. Significant effect of the meal on all 4 variables ($P \leq .01$). N = 25.

Appetite scores were significantly changed after the ingestion of the standardized breakfast meal (Fig. 1). A significant effect of time was noted for all appetite scores ($P < .001$). As displayed in Fig. 2, significant effects of time for both total ghrelin (Fig. 2A) and total PYY (Fig. 2B) were also observed in the postprandial period ($P < .001$). Total ghrelin reached its lowest concentrations at 60 minutes postprandially, at which point it was 22% below fasting values, whereas PYY was increased 76% over fasting values at 120 minutes.

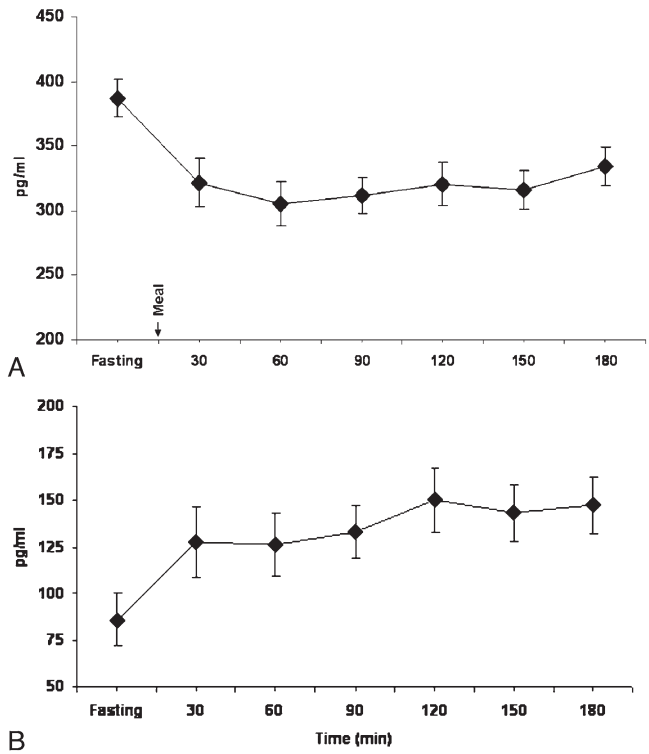

Fig. 2. Total ghrelin (A) and total PYY (B) fasting and for 3 hours after a standardized breakfast. Significant effect of time for total ghrelin and PYY ($P \leq .01$). N = 24.

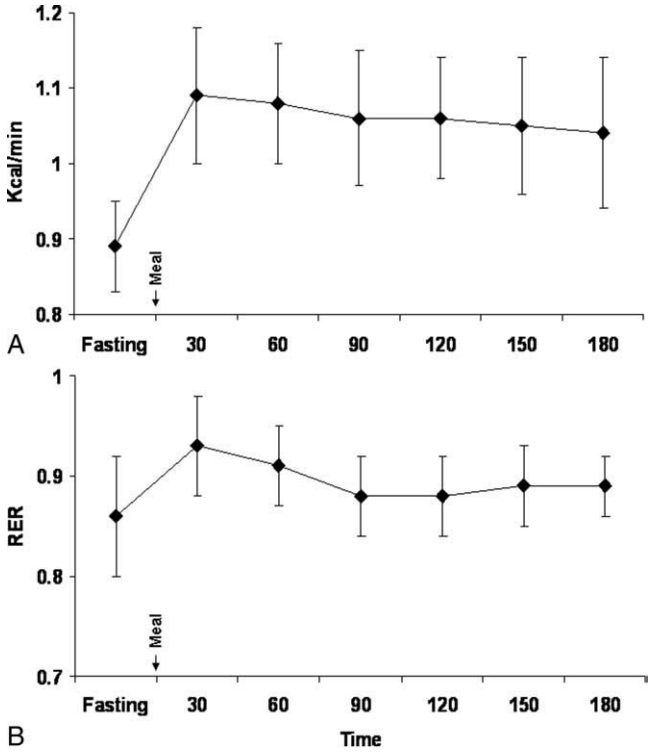

Fig. 3. Energy expenditure (EE) (A) and RER (B) fasting and for 3 hours after a standardized breakfast. Significant effect of time for PEE and RER ($P \leq .01$). N = 24.

As expected, there were significant changes for both PEE ($P < .001$) and RER ($P < .001$) over the 3-hour postprandial follow-up (Fig. 3). Cumulative PEE for the 180-minute postprandial period was 190.0 ± 16.1 kcal, whereas TEF for the same period was 30.0 ± 12.0 kcal.

Energy intake during the ad libitum buffet-style meal was 533.9 ± 252.3 kcal. The macronutrient intake consisted of 67.9 ± 32.1, 18.9 ± 12.9, and 24.1 ± 11.1 g of carbohydrates, lipids, and proteins, respectively (Table 2).

No significant associations were noted between prelunch (time 180 minutes) and area under the curve (AUC) (trapezoid method) for total ghrelin and PYY and ad libitum EI at lunch time (results not shown). In addition, the only significant correlation between appetite scores and the 2 peptides assayed was AUC ghrelin with AUC PFC (r = −0.36, $P < .05$). In contrast, prelunch appetite scores and AUC of these same appetite scores were consistent correlates of both total caloric intake and macronutrient intake (particularly lipid intake) during the ad libitum lunch (Table 3).

Table 2
Energy intake and macronutrient composition at the ad libitum buffet-style meal

Variables	Mean	Range
EI (kcal)	537.5 ± 250.1	134.6-939.3
Carbohydrates (g)	67.9 ± 32.1	12.5-134.3
%	52.0 ± 11.7	24.6-85.0
Lipids (g)	18.9 ± 12.9	1.1-58.3
%	29.5 ± 10.3	7.2-55.9
Proteins (g)	24.1 ± 11.1	2.6-55.6
%	18.6 ± 6.3	7.8-29.8

Values are means ± SD. N = 25. Body weight was obtained with the scale.

Table 3
Correlation analyses between prelunch (180 minutes) and AUC VAS scores and energy and macronutrient intake from the ad libitum buffet-style meal

	Kilocalories	Lipids	CHO	Proteins
Desire to eat				
180 min	0.37*	0.39*	0.20	0.47*
AUC	0.39*	0.51†	0.16	0.45*
Hunger				
180 min	0.39*	0.38*	0.26	0.45*
AUC	0.42*	0.53†	0.18	0.46*
Fullness				
180 min	−0.51†	−0.49†	−0.37*	−0.54†
AUC	−0.38*	−0.46*	−0.15	−0.51†
PFC				
180 min	0.37*	0.39*	0.21	0.45*
AUC	0.38*	0.48†	0.15	0.43*

N = 25. CHO indicates carbohydrates.
* P value ≤ .05.
† P value ≤ .01.

Significant correlations were noted between total PYY and PEE as well as between total PYY and TEF (Fig. 4). In our study, body weight was more closely related to TEF than was fat-free mass (results not shown). As the main objective was related to investigate the potential association between total PYY and TEF, partial correlations were performed controlling for body weight. As shown in Table 4, PEE and TEF were significantly and consistently correlated with PYY at times 60 ($r = 0.37$, $P \leq .05$ and $r = 0.41$, $P \leq .05$), 90 ($r = 0.36$, $P \leq .05$ and $r = 0.33$, $P \leq .1$), 120 ($r = 0.51$, $P \leq .01$ and $r = 0.43$, $P \leq .05$), 150 ($r = 0.42$, $P \leq .05$ and $r = 0.40$, $P \leq .05$), and 180 minutes ($r = 0.34$, $P \leq .1$ and $r = 0.35$, $P \leq .05$). In addition, AUC PYY was also a significant correlate of total PEE ($r = 0.41$, $P \leq .05$) and total TEF ($r = 0.41$, $P \leq .05$). Peptide YY was also negatively related to RER at all time points, but this association was only significant at time 90 ($r = -0.41$, $P \leq .05$). Partial correlations between fasting PYY and REE ($r = 0.13$, not significant) or RER ($r = 0.25$, not significant) were not statistically significant. Finally, no significant associations were noted between ghrelin, PEE, and RER (results not shown).

4. Discussion

The main findings of this study are 3-fold. First, appetite scores are more consistent correlates of ad libitum EI than are total ghrelin and total PYY. Second, appetite scores are not related to total PYY or total ghrelin under normal physiologic conditions. Third, PYY is a significant and consistent correlate of both PEE and TEF. To our knowledge, this is the first study to report that postprandial levels of total PYY may be associated to TEF.

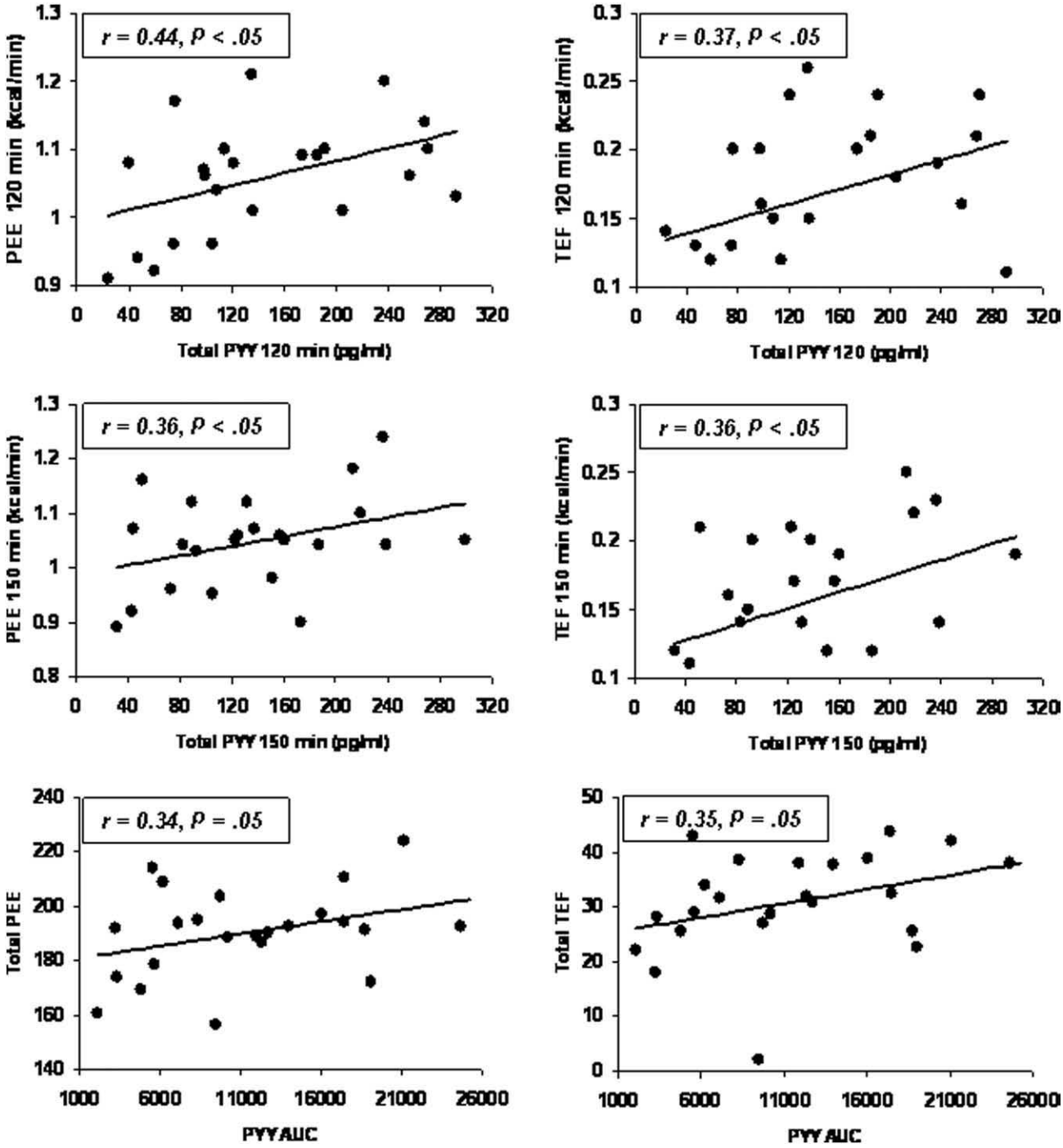

Fig. 4. Simple correlation coefficients between PYY and PEE and TEF at time points 120 and 150 minutes and between PYY AUC and total PEE and TEF. Total PEE and TEF = total EE and EE over resting values for 180 minutes after the ingestion of the standardized breakfast, respectively. N = 23.

Our results indicate that preprandial appetite scores are correlates of EI. Although controversy remains [28], results from different studies [29-31] have shown that appetite scores predict EI to various degrees. In contrast, we did not observe any significant associations between total ghrelin and PYY and EI. This is supported by at least 1 other study in which no association was found between PYY and daily caloric intake [23]. This latter observation is nonetheless surprising given the anorectic effects of PYY and the orexigenic effects of ghrelin. This may be explained by the fact that most of the studies that have documented a link between ghrelin [15] and/or PYY [9,32] and appetite scores and EI used exogenous administration of these peptides. According to recent studies, it would seem that circulating levels of PYY 3-36 need to reach 60 pmol/L to exert significant effects on EI, which represents an approximately

Table 4
Partial correlation analyses (controlling for body weight) between PYY and energy metabolism variables at corresponding time point

	PEE	TEF	RER
PYY 30 min	0.29‡	0.32‡	−0.24
PYY 60 min	0.37*	0.41*	−0.26
PYY 90 min	0.36*	0.33‡	−0.41*
PYY 120 min	0.51†	0.43*	−0.35‡
PYY 150 min	0.42*	0.40*	−0.29‡
PYY 180 min	0.34‡	0.35*	−0.13
PYY AUC	0.41*	0.41*	−0.33‡

n = 23.
* P value ≤ .05.
† P value ≤ .01.
‡ P value ≤ .1.

3- to 4-fold increase over values observed upon nutrient stimulation only [10,11]. In the present study, total ghrelin was reduced by 22% and total PYY increased by 76% in response to food ingestion. Such variations may not be sufficient to induce concomitant changes in appetite ratings. It then may be that the magnitude of changes needed for either ghrelin or PYY to elicit changes in appetite and/or caloric intake may very well exceed those variations observed under normal physiologic stimuli in nonobese healthy subjects.

It was recently reported that fasting PYY was correlated to satiety (calculated over a 3-hour period) [23]. We did not find any such relationships. There are some discrepancies between the 2 studies that should be noted. Even if the sampling periods were 3 hours and the total PYY was measured in both studies, subjects in the previous study included both men and women, they were predominantly overweight or obese (BMI = 30.0 ± 1.3 kg/m^2), and the caloric intake of the standardized breakfast was adjusted to body weight. Because PYY secretion has been shown to be blunted in obese subjects [9] and also to be proportional to caloric intake [33], these study differences complicate the comparison of the results. At this point, it is too early to conclude whether variations of PYY under normal physiologic conditions have an influence on the expression of appetite such as measured with a VAS.

With respect to a link between PYY and energy metabolism, to our knowledge, 4 studies have investigated this matter [12,20,21,23]. In the first 2 studies, it was shown that long-term PYY 3-36 administration altered substrate partitioning, favoring increased fat oxidation in rats [21] and mice [20] in the absence of changes in EE. More recently, Sloth et al [12] investigated whether short-term subcutaneous administration of both PYY 1-36 and 3-36 could alter energy metabolism and substrate partitioning. The results showed for the first time in human subjects that PYY 3-36 increases EE and fat oxidation rates.

Whether supraphysiologic variations in PYY levels are needed to elicit changes in EE and fat oxidation is still unknown. Guo and colleagues [23] recently reported a negative correlation between fasting PYY levels and 24-hour RER, as well as a negative relationship between a 15-hour resting metabolic rate measurement and fasting PYY. Although interesting, the authors correlated total PYY values and EE measures that were not necessarily taken during the same time frame. In addition, PYY 3-36 is lowest before meals; and this value may not represent the best correlate of its potential effects on daily energy metabolism. In our study, total PYY was sampled within the same time frame as PEE and TEF during a 3-hour postprandial follow-up. Our results show consistent associations between postprandial PYY levels and both PEE and TEF after appropriate control for the confounding effects of body weight. There is evidence to support that PYY 3-36 may influence EE. Peptide YY 3-36 is most abundant postprandially [34] and binds with more affinity to Y2 receptor [35,36], which activates arcuate pro-opiomelanocortin neurons [37,38] and in turn the melanocortin system. It has also been shown that melanocortin receptor agonists produce an elevation in EE [39] and an activation of sympathetic nervous system (SNS) activity [40]. Finally, the facultative component of TEF is modulated mainly through the increase of SNS activity and its resulting activation of β-adrenergic pathways [41,42]. It is thus reasonable to postulate that the increase in PYY 3-36, such as seen postprandially, could increase SNS activity and in turn TEF. Although the relationship between PYY and TEF does present interesting insights, our results do not allow us to allude to a causal relationship.

In summary, results from this study demonstrate that neither total ghrelin nor total PYY is correlated with appetite scores or EI in healthy normal-weight women. A corollary of this observation is that these peptides are likely not good proxies of feeding behavior under normal physiologic conditions in this population. Our results also suggest that PYY may influence PEE. Nonetheless, more detailed investigations will be needed to establish a causal link between PYY in energy metabolism.

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