

Effect of Human Body Weight Changes on Circulating Levels of Peptide YY and Peptide YY_{3–36}

P. T. Pfluger,* J. Kampe,* T. R. Castaneda, T. Vahl, D. A. D'Alessio, T. Kruthaupt, S. C. Benoit, U. Cuntz, H. J. Rochlitz, M. Moehlig, A. F. H. Pfeiffer, C. Koebnick, M. O. Weickert, B. Otto, J. Spranger, and M. H. Tschöp

Departments of Psychiatry and Medicine (P.T.P., J.K., T.R.C., T.V., D.A.D., T.K., S.C.B., M.H.T.), Obesity Research Center, University of Cincinnati–Genome Research Institute, Cincinnati, Ohio 45237; Department of Physiology (J.K.), Monash University, Melbourne 3800, Australia; Center for Psychosomatic Medicine (U.C.), D-83209 Prien, Germany; German Institute of Human Nutrition (H.J.R., M.M., A.F.H.P., C.K., M.O.W., J.S.), 10551 Nuthetal, Germany; Department of Preventive Medicine (C.K.), University of Southern California, Los Angeles, California 90089; and Department of Gastroenterology (B.O.), University Hospital, D-81377 Munich, Germany

Background: Recent findings suggest that low plasma peptide YY (PYY) levels may contribute to diet-induced human obesity and justify PYY replacement therapy. Although the pharmacological value of PYY is controversial, further study of the secretion of the precursor PYY_{1–36} and the pharmacologically active PYY_{3–36} is indicated to determine the potential role in energy balance regulation.

Aim: Our objective was to determine the effects of acute and chronic changes in human body weight on circulating levels of the putative satiety hormone peptide YY.

Design: Total plasma PYY levels (PYY_{1–36} + PYY_{3–36}) were measured in 66 lean, 18 anorectic, 63 obese, and 16 morbidly obese humans. In addition, total PYY was measured in 17 of the obese patients after weight loss and in the 18 anorectic patients after weight gain. Fasting PYY_{3–36} levels were measured in 17 lean and 15 obese individuals.

Results: Fasting total plasma PYY levels were highest in patients with anorexia nervosa (80.9 ± 12.9 pg/ml, $P < 0.05$) compared with lean (52.4 ± 4.6 pg/ml), obese (43.9 ± 3.8 pg/ml), or morbidly obese (45.6 ± 11.2 pg/ml) subjects. In obese patients, weight loss of 5.4% was associated with a 30% decrease in fasting total PYY plasma levels. In anorectic patients, weight gain had no effect on fasting PYY. PYY_{3–36} levels did not differ between lean (96.2 ± 8.6 pg/ml) and obese (91.5 ± 6.9 pg/ml) subjects.

Conclusion: Our findings do not support a role for abnormal circulating PYY in human obesity. We conclude that circulating PYY levels in humans are significantly elevated in anorexia nervosa and, given the controversially discussed anorectic effect of PYY, could theoretically contribute to that syndrome. (*J Clin Endocrinol Metab* 92: 583–588, 2007)

PEPTIDE YY (PYY) is an intestinal peptide that has been advanced as a satiety factor (1–3). PYY belongs to the pancreatic polypeptide family, which includes pancreatic polypeptide (PP) and neuropeptide Y (NPY). These related peptides display a high sequence homology and share a common tertiary structure (PP-fold). PYY mRNA has been identified in the intestine and the pancreas, and, like many other gastrointestinal hormones, it can be detected in distinct brainstem neurons (4). The peptide is predominantly secreted into circulation by endocrine L cells, which line the distal small bowel and colon.

PYY is metabolized by the enzyme dipeptidyl peptidase-IV, which hydrolyzes PYY at the Pro2-Ile3 bond, converting a precursor form PYY_{1–36} to PYY_{3–36} (5, 6). Because of the extent and rapidity of this process, the main circulating form of PYY in postprandial human plasma is PYY_{3–36} (5). Both forms of PYY bind to the Y2 isoform of the NPY receptor (7,

8). PYY_{1–36} also binds the Y1 and Y5R isoforms (8). Both PYY_{1–36} and PYY_{3–36} inhibit gastric acid and pancreatic enzyme secretion and suppress gastrointestinal motility (9–14). Similar to NPY, PYY_{1–36} and PYY_{3–36} are potent stimuli for feeding in the brain, producing massive and immediate hyperphagia when injected into cerebral ventricles, the paraventricular nucleus, or the hippocampus (15).

In contrast to the effects in the central nervous system, Batterham and Bloom (1) reported that circulating PYY_{3–36} is an endogenous satiety factor, mediating this effect through the Y2R subtype. In these experiments, iv PYY_{3–36} suppressed food intake in rodents and humans and decreased body weight gain in rodents (3). These observations were hailed as a potential advance toward an effective antiobesity treatment (2). This finding has not been universally confirmed, and 12 independent study groups recently reported that they were unable to reproduce any anorexigenic or weight-reducing effects of PYY_{3–36} in rodents (16).

There is little published information on plasma levels of PYY in response to changes in energy balance. PYY levels reach a nadir after fasting and increase after meals. Over the course of a day, PYY levels are lowest in the morning and increase steadily after breakfast, lunch, and the evening meal (17). After ingestion of a test meal, plasma levels increase

First Published Online November 21, 2006

* P.T.P. and J.K. contributed equally to this work.

Abbreviations: BMI, Body mass index; CV, coefficient(s) of variation; NPY, neuropeptide Y; PYY, peptide YY.

JCEM is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

proportionally to the amount of ingested calories within 15 min, reaching a peak at approximately 90 min, and then remain elevated for up to 6 h (14). To determine the effects of chronic energy balance on plasma PYY, we compared circulating PYY_{1–36} and PYY_{3–36} levels in plasma of anorectic, lean, obese, and morbidly obese subjects.

Patients and Methods

Anorexia patients

Plasma samples from 18 female patients [body mass index (BMI), 15.4 ± 0.3 kg/m²; age, 25.6 ± 1.0 yr] with anorexia nervosa according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV, American Psychiatric Association, 1994) were measured in this study. The patients had been admitted to a psychosomatic treatment center (Klinik Rosenneck, Prien, Germany) for an inpatient intervention program. All patients had been examined and were in good health apart from their eating disorder. Fasting blood samples were taken at three different times: 1) within the first 3 d after admission (no weight gain since admission or in the last 2 wk before), 2) after a weight gain of at least 2 kg twice consecutively when weighing the patients twice a week (1–7 wk after admission), 3) in the last week before discharge [6–19 (mean, 10.6 ± 0.8) wk in hospital]. None of the patients received parenteral nutritional support at any time of the treatment. The procedure was reviewed and approved by the ethics committee of the Medical Faculty of the Ludwig-Maximilians-University, Munich, Germany.

Lean, obese, and morbidly obese individuals

Fasting blood samples from 66 lean individuals (24 males, 42 females; BMI, 22.1 ± 0.2 kg/m²; age, 41.5 ± 2.2 yr), 63 obese individuals (20 males, 43 females; BMI, 32.7 ± 0.3 kg/m²; age, 48.4 ± 2.4 yr), and 16 morbidly obese individuals (one male, 15 females; BMI, 44.5 ± 0.9 kg/m²; age, 44.7 ± 2.8 yr) were drawn at the Department of Clinical Nutrition at the German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany. In addition, PYY_{3–36} was measured in 17 lean (all female; BMI, 22.0 ± 0.5 kg/m²; age, 51.6 ± 1.9 yr) and 15 obese (all female; BMI, 31.1 ± 0.5 kg/m²; age, 52.0 ± 2.0 yr) individuals. For another subset of obese subjects (three males, 14 females; BMI, 35.1 ± 1.4 kg/m²) blood samples were drawn approximately 12 wk after undergoing a therapeutic weight loss program (average Δ BMI, -1.9 kg/m²; 5.4%; $P < 0.001$). BMI was classified according to World Health Organization and Centers for Disease Control criteria: normal BMI, 18.5–25 kg/m²; overweight BMI, 25–30 kg/m²; obese BMI, 30–40 kg/m²; morbidly obese BMI, more than 40 kg/m² (18, 19). All patients gave written informed consent for their participation in the study, which was approved by the Ethical Committee of the University Potsdam.

Meal study

PYY_{1–36} and PYY_{3–36} were measured after ingestion of water or a high-caloric-density meal in six lean, healthy volunteers (three male, three female; age, 29.0 ± 1.2 yr; BMI, 20.7 ± 1.1 kg/m²). On two consecutive days, blood samples were taken before and after a test ingestion (–5, 0, 15, 30, 60, 90, and 120 min), starting at 0900 h. On 1 d, 250 ml water was consumed. On the second day, a high-calorie meal [Burger King Croissan'wich with ham, cheese, and eggs, hash brown rounds, orange juice, and one can of Ensure Plus (Abbott, Chicago, IL); total, 1030 kcal] was consumed within 15 min and blood sampled as described above. This study was reviewed and approved by the Human Subjects Committee at the University of Cincinnati.

Measurement of total PYY

Blood samples were drawn into EDTA tubes in the morning after an overnight fast of 12 h, the plasma separated within 1 h by centrifugation at $3000 \times g$ and 4°C and stored at -80°C . Human total PYY plasma levels were measured using an ELISA kit (ACTIVE Total Peptide YY) from Diagnostic Systems Laboratories (Webster, TX). The ELISA quantifies both PYY_{1–36} and PYY_{3–36}. The cross-reactivity against mouse PYY_{1–36}

and human PYY_{1–36} is 100%. Intra- and interassay coefficients of variation (CV) are less than 3.3 and 7.6%, respectively. The sensitivity (minimum detection limit), as calculated by interpolation, is 9.5 pg/ml. All measurements were performed in duplicate according to the manufacturer's instructions.

Measurement of PYY_{3–36}

For specific measurement of PYY_{3–36}, blood samples were drawn after an overnight fast into chilled tubes containing EDTA and a protease inhibitor (Trasylol, 500 kIU/ml; Bayer, Leverkusen, Germany) and centrifuged at $3000 \times g$ and 4°C. For quantification of PYY_{3–36}, a RIA from Linco [human PYY(3–36) Specific RIA Kit; Linco Research, St. Charles, MO] was used. The assay specifically detects human PYY_{3–36} and has no detectable cross-reactivity with human PYY_{1–36}. Intra and interassay CV are less than 11.0 and 15.0%, respectively, and the lowest level of PYY_{3–36} that can be detected is 20 pg/ml. All measurements were performed in duplicate according to the manufacturer's instructions.

Measurement of leptin and leptin-binding protein

Blood samples were drawn into EDTA tubes in the morning after an overnight fast of 12 h, the plasma separated within 1 h by centrifugation at $3000 \times g$ and 4°C and stored at -80°C . Human leptin and human leptin-binding protein were measured by using ELISA kits (Active Human Leptin and Active Leptin Soluble Receptor, respectively) from Diagnostic Systems Laboratories. For the detection of leptin, no cross-reactivity was observed with bovine or porcine sera as well as with human leptin fragments LP 1 (5–21), LP 2 (22–42), LP 3 (61–85), and LP 4 (114–146). Recombinant leptin was shown to have no cross-reactivity in the leptin-binding protein ELISA. Intra- and interassay CV were less than 6.2 and 5.3% for the determination of leptin and less than 13.3 and 9.6% for the determination of leptin-binding protein, respectively. The theoretical sensitivity (minimum detection limit) of the assays, as calculated by interpolation, was 0.05 ng/ml for leptin and 0.14 ng/ml for leptin-binding protein. All samples were measured in duplicate according to the manufacturer's instructions.

Statistical analysis

BMI and PYY levels of anorectic, control, obese, and morbidly obese subjects were compared using one-way ANOVA followed by Dunnett's *post hoc* test. Significant changes of BMI and PYY levels in obese subjects subjected to weight loss and anorectic patients on weight-gain therapy were analyzed by paired *t* tests and repeated-measures ANOVA with *post hoc* Bonferroni's multiple comparison tests, respectively. BMI and PYY_{3–36} levels in the additional sets of control and obese patients were compared by unpaired (two-tailed) *t* tests. Differences in the fasting or postprandial release of total PYY and PYY_{3–36} were examined by two-way ANOVA followed by Bonferroni's multiple comparison tests. Correlations of PYY levels with age, BMI, leptin, and leptin-binding protein levels were analyzed by two-tailed Pearson correlation. All statistical analyses were performed using GraphPad Prism version 4.0 (GraphPad Software, San Diego, CA). Results are presented as means \pm SEM or as individual levels with median values.

Results

Elevated total PYY plasma levels in anorexia nervosa

Fasting plasma total PYY in patients with anorexia nervosa were 80.9 ± 12.9 pg/ml ($n = 18$, all females; BMI, 15.4 ± 0.3 kg/m²). These values were higher than levels in healthy control individuals (PYY, 52.4 ± 4.6 pg/ml, $P < 0.05$; $n = 66$, 24 males, 42 females; BMI, 22.1 ± 0.2 kg/m²) (Fig. 1). In response to weight gain during hospitalization (Δ BMI, $+2.8$ kg/m²; Δ body weight, $+7.6 \pm 0.5$ kg), plasma PYY levels did not change significantly ($P = 0.55$) during weight gain (PYY, 101.9 ± 16.4 pg/ml; BMI, 16.4 ± 0.3 kg/m²) and after therapy (PYY, 96.1 ± 12.4 pg/ml; BMI, 18.2 ± 0.4 kg/m²) (Fig. 2A; $P < 0.05$).

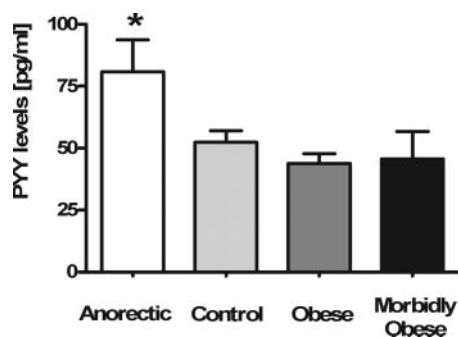


FIG. 1. Total PYY plasma levels in obesity and anorexia nervosa. Total PYY plasma levels (pg/ml) of obese ($n = 63$) and morbidly obese ($n = 16$) patients do not differ from those of lean individuals ($n = 66$), but total PYY is increased in anorexia nervosa patients ($n = 18$). *, $P < 0.05$. Results are shown as mean \pm SEM.

Total PYY plasma levels in obesity and morbid obesity

Total PYY plasma levels of patients with obesity (PYY, 43.9 ± 3.8 pg/ml; $n = 63$, 20 males, 43 females; BMI, 32.7 ± 0.3 kg/m²) or morbid obesity (PYY, 45.6 ± 11.2 pg/ml; $n = 16$, one male, 15 females; BMI, 44.5 ± 0.9 kg/m²) did not differ from levels of healthy control individuals (PYY, 52.4 ± 4.6 pg/ml; $n = 66$, 24 males, 42 females; BMI, 22.1 ± 0.2 kg/m²; $P > 0.05$) (Fig. 1). In response to therapeutic weight loss during an 8-wk outpatient weight-loss program (mean Δ BMI, -1.9 kg/m²; $P < 0.0001$; $n = 17$, three males, 14 females), total PYY plasma levels of obese subjects decreased

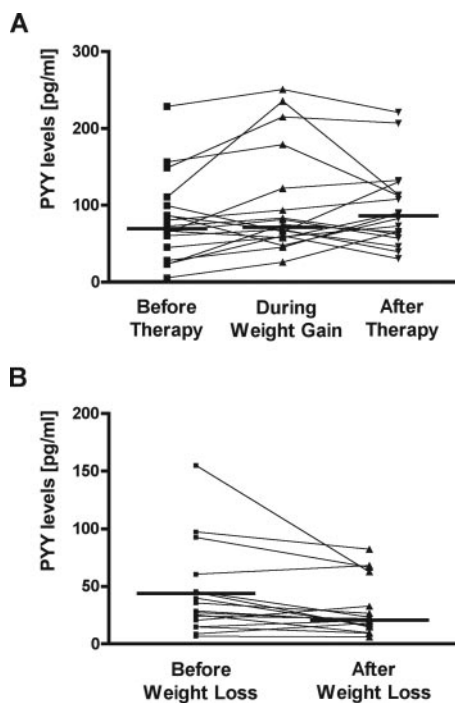


FIG. 2. Effect of weight changes in anorexia nervosa and obese patients on total PYY plasma levels. A, Individual and median total PYY plasma levels (pg/ml) of anorexia nervosa patients ($n = 18$) before, during, and after therapeutic weight gain during a stay in a hospital specializing in the diagnosis and treatment of anorexia nervosa and psychosomatic diseases. B, Individual and median total PYY plasma levels (pg/ml) of obese patients ($n = 17$) before and after weight loss during an 8-week outpatient weight-loss program.

significantly from 43.8 ± 9.4 to 30.8 ± 5.7 pg/ml ($P = 0.04$; Fig. 2B).

PYY₃₋₃₆ plasma levels in lean and obese individuals

Fasting plasma levels of PYY₃₋₃₆ were 91.5 ± 6.9 pg/ml in obese female subjects ($n = 17$; BMI, 31.1 ± 0.5 kg/m²) and did not differ from a group of lean female controls (96.2 ± 8.6 pg/ml; $n = 17$; BMI, 22.0 ± 0.5 kg/m²; $P = 0.68$) (Fig. 3).

Relationship between plasma PYY levels, BMI, age, leptin levels, and leptin-binding protein levels in humans

Total PYY plasma levels in anorectic, normal, obese, and morbidly obese individuals are weakly associated with BMI ($r = -0.1820$; $P = 0.0201$; $n = 163$) (Fig. 4A) and plasma levels of leptin-binding protein ($r = 0.3643$; $P = 0.0226$) (Fig. 4D) but not with circulating leptin levels ($r = -0.0961$; $P = 0.5606$; $n = 39$) (Fig. 4C) or age ($r = 0.0713$; $P = 0.6887$; $n = 34$) (data not shown). PYY₃₋₃₆ levels are not associated with BMI ($r = -0.1132$; $P = 0.5238$; $n = 34$) (Fig. 4B) or age ($r = 0.0813$; $P = 0.6474$; $n = 34$; data not shown).

A high-calorie meal increases human plasma PYY levels

To determine the performance of our total PYY and PYY₃₋₃₆ assays in a setting where plasma PYY levels have been established, we studied a group of lean controls before and after a meal. After a high-calorie breakfast (1030 kcal), both total PYY plasma levels (Fig. 5A) and PYY₃₋₃₆ levels (Fig. 5B) significantly increased by 208% (total PYY, from 81.8 ± 19.5 to 170.3 ± 18.7 pg/ml after 120 min) and 125% (PYY₃₋₃₆, from 164.7 ± 10.5 to 206.2 ± 9.5 pg/ml after 120 min) in overnight fasted healthy human volunteers ($n = 6$; three males, three females; BMI, 20.7 ± 1.1 kg/m²; age, 29.0 ± 1.2 yr), as expected ($P < 0.0001$). On a control day without ingesting a breakfast, total PYY and PYY₃₋₃₆ levels in the same overnight fasted healthy volunteers did not change (from 82.2 ± 20.9 to 62.1 ± 29.2 pg/ml and 147.4 ± 8.1 to 142.7 ± 11.7 pg/ml after 120 min, respectively).

Discussion

The initial excitement over the identification of the satiety-inducing hormone leptin (20, 21) or the hunger-promoting hormone ghrelin (22, 23) was rapidly limited by the sobering discovery that in obese humans, circulating levels of leptin are high (24) and blood levels of ghrelin are low. Such coun-

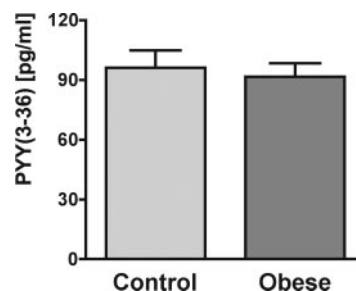
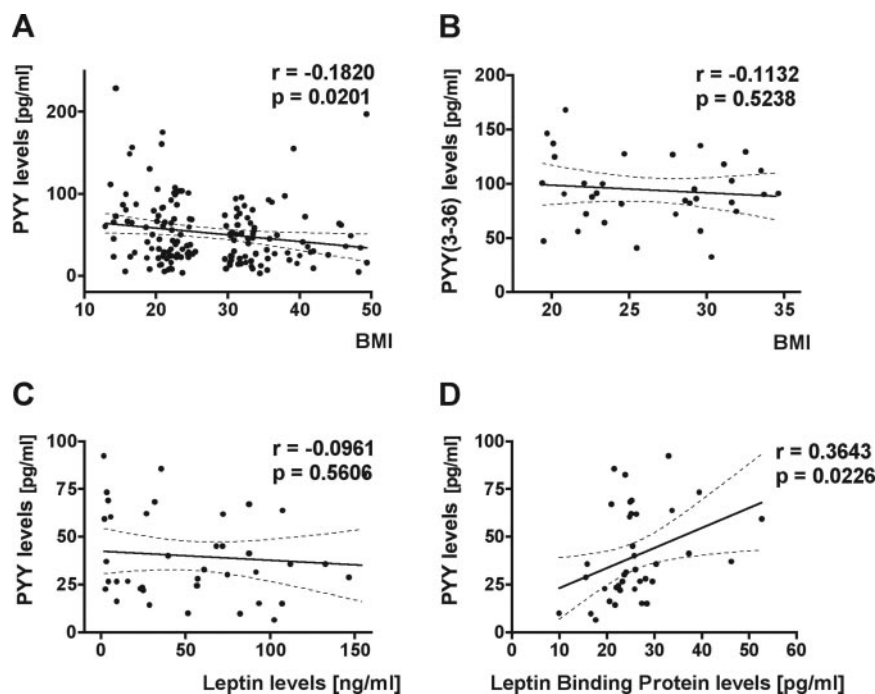


FIG. 3. PYY₃₋₃₆ plasma levels in a subset of lean controls ($n = 17$) and obese subjects ($n = 15$). Plasma samples were treated with 500 kIU aprotinin to inhibit proteolytic cleavage of (inactive) PYY₁₋₃₆ into (active) PYY₃₋₃₆. Results are shown as mean \pm SEM.

FIG. 4. Relationship between total PYY with BMI, leptin, and leptin-binding protein and PYY_{3–36} with BMI. A and B, Weak inverse correlation between total PYY plasma levels (pg/ml) and BMI ($n = 163$; $r = -0.1820$; $P = 0.0201$) (A) but no correlation between PYY_{3–36} plasma levels (pg/ml) and BMI ($n = 34$; $r = -0.1132$; $P = 0.5238$) (B). C, No correlation between total PYY plasma levels (pg/ml) and leptin plasma levels ($n = 39$; $r = -0.0961$; $P = 0.5606$). D, Weak correlation between total PYY plasma levels (pg/ml) and leptin-binding protein (soluble extracellular domain of ObR-b) ($n = 39$; $r = 0.3643$; $P = 0.0226$).



terintuitive findings indicated that human obesity could not be explained by hypoleptinemia or hyperghrelinemia but rather caused resistance syndromes and compensatory processes leading to hyperleptinemia and hypoghrelinemia. Hope for a simple explanation and solution for obesity rose again when two more recent publications reported not only that the gut hormone PYY_{3–36} decreased food intake and

body weight gain in rodents (3) but also that levels of PYY were found to be significantly lower in obese patients (2). The authors of those studies proposed that a PYY deficiency could contribute to the genesis of obesity in humans and raised the possibility that a PYY replacement therapy might cure the disease along with its devastating consequences such as diabetes and cardiovascular diseases.

In fact, follow-up studies have indicated that the body-weight-reducing effects of PYY_{3–36} are limited (7, 16), suggesting that obesity is not simply a PYY-deficient state. Consistent with that inference, our large series of measurements in obese subjects indicate that PYY plasma levels are not low but normal in established obesity. Initial studies that had detected PYY deficiency in obese humans used immunoassays that recognized total PYY, a measure that includes both PYY_{1–36} and PYY_{3–36} (2). Using the same approach, we found a significant but very weak inverse correlation of BMI levels with PYY levels. However, we were unable to find low levels of PYY in by far the largest population of obese and morbidly obese individuals where PYY levels have been studied to date. Therefore, a weak negative association between circulating PYY and BMI may not be a functionally meaningful observation.

Nevertheless, it would be theoretically possible that the putatively satiety-inducing fraction of circulating PYY, PYY_{3–36}, could be decreased specifically in obesity. If at the same time PYY_{1–36} levels would be increased in obesity, a causal role for PYY in obesity would become plausible again. We therefore also specifically examined plasma concentrations of PYY_{3–36} in obese patients and control subjects using an immunoassay that does not recognize PYY_{1–36}. PYY_{3–36} is the form of PYY that has been proposed to possess satiety-inducing effects due to its relative specificity for hypothalamic NPY-Y2 autoreceptors. We collected samples from a subset of obese and lean individuals and treated the samples

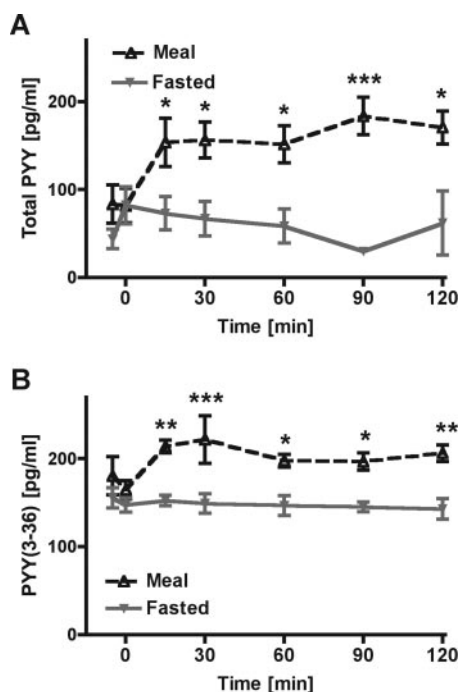


FIG. 5. Increased PYY levels after high-calorie meal indicate assay validity. Total PYY (A) and PYY_{3–36} (B) plasma levels (pg/ml) significantly increased for 2 h after ingestion of a high-calorie breakfast in six healthy volunteers. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. Results are shown as mean \pm SEM.

with a protease inhibitor to prevent *ex vivo* metabolism of PYY_{1–36} and mask PYY_{3–36} deficiency in human obesity. However, no difference was found between PYY_{3–36} levels from obese and lean individuals.

How can the discrepancies between these observations and the original findings by Batterham *et al.* (2) be explained? One possibility would be that there are significant differences between the quantification methods used. Relative changes or differences in plasma PYY levels are likely to be solidly detectable if quantified with the same immunoassay within one experiment. However, it is unclear whether absolute concentrations of total PYY or specific PYY_{3–36} can be quantified with the currently available immunoassays. To date, although various suppliers offer PYY detection kits, no gold standard exists for the measurement of total PYY or PYY_{3–36} plasma levels; comparisons between PYY measurements therefore have to be evaluated with caution. To overcome this obstacle, we not only used very well established and tested commercially available immunoassays, but we also performed additional validation studies showing that both assays detected the typical increase of PYY after a high-calorie meal. Those validation studies add additional evidence that both of our quantification methods were measuring exactly what the manufacturer indicated. Interestingly, the same group that first reported PYY deficiency in obesity (2) more recently published that in a different population of obese patients and healthy controls, they were now unable to repeat their initial observations and did not detect any differences in baseline PYY concentrations using the same immunoassay (25). Similarly, another independent study group recently reported a lack of correlation between PYY levels and BMI (26).

It is possible that the small size ($n = 12$) of the population in the study first reporting low PYY levels in obesity led to results that cannot be repeated in larger populations. That conclusion is consistent with reports by another group of investigators (27), who while studying the effect of gastric bypass surgery on circulating levels of PYY were also unable to detect differences of PYY concentrations between obese and lean individuals. Of course, the populations of currently available studies on PYY in obesity all slightly differ regarding their age and gender as well as their degree of obesity. In addition, a differing food composition between anorectic, lean, and obese subpopulations as well as internationally diverse dietary habits may contribute to explain the discrepancies in the reports on PYY levels. For instance, in rats, a higher release of PYY was demonstrated after ingestion of a fiber-rich diet (28, 29). In humans, either a protein-rich or carbohydrate-rich diet was more effective in increasing PYY release than a high-fat diet (30). However, all studies have based their findings on comparisons with well-matched control groups, and variations in diet composition/dietary habits were not reported. These findings make it less likely that the above mentioned variabilities are the cause for entirely different results. Baseline PYY concentrations therefore seem to be unchanged in obese subjects compared with lean controls. Very recent reports suggest an absent or blunted PYY release upon ingestion of a meal in both obese subjects (31, 32) and patients with bulimia nervosa (33). Whether an at-

tenuated response bears any physiological consequences still remains unclear but may deserve further attention.

Another interesting observation from our studies is that PYY levels seem to be higher in some patients with anorexia nervosa. These findings are consistent with recent reports from another laboratory using another immunoassay (34) but stand in contrast to reports from another group that was unable to find any differences of baseline PYY levels between anorexia nervosa patients and control subjects (25). Although it is theoretically possible that increased levels of PYY may play a role in a subset of patients with anorexia nervosa, we do observe a very high degree of interindividual variability within the subjects we examined. Furthermore, the here observed high PYY levels might be a consequence of the combination of young age and female gender of this specific subset of patients studied (26, 35). Therefore, we believe that future studies of the regulation of PYY secretion in patients with eating disorders are needed to establish a causal relationship.

In a small subset of obese individuals, total PYY levels were significantly reduced in response to weight loss. However, in view of the only very weak inverse association of BMI with total PYY (but not PYY_{3–36}) levels, it seems unlikely that the observed reduction of PYY levels in obese subject after weight loss can be explained by body composition changes. In our subset of anorexia nervosa patients on a weight-gain therapy, a chronic positive energy balance did not alter circulating total PYY levels. However, the study of larger cohorts of anorectic or obese patients that are subjected to weight gain or weight loss could help to clarify whether a temporary or chronic change of energy balance can affect PYY levels, *e.g.* via central nervous pathways. A first very recent report showed that 48 or 72 h fasting in lean humans significantly decreased both BMI and PYY levels (36).

In conclusion, our results show that PYY does not appear to be pathologically decreased in human obesity and so must be questioned as a cause for the maintenance of overweight. Nevertheless, there are still a number of open questions regarding PYY, including a possible role in anorexia nervosa and related eating disorders. Only a thorough understanding of the details involved in endocrine energy balance regulation will allow for the separation between essential players and redundant mechanisms and ultimately lead to an efficient and safe antiobesity drug. The insight that there may be no PYY deficiency in human obesity may be a small step back from earlier proposed hypotheses, but based on currently available data, it might be a step in the right direction.

Acknowledgments

Received July 5, 2006. Accepted November 15, 2006.

Address all correspondence and requests for reprints to: Matthias H. Tschöp, M.D., Associate Professor, Departments of Psychiatry and Medicine, University of Cincinnati, Office E-217, Genome Research Institute, 2170 East Galbraith Road, Cincinnati, Ohio 45237. E-mail: tschoemh@ucmail.uc.edu.

Disclosure Statement: The authors have nothing to disclose.

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