0013-7227/06/$15.00/0
Printed in U.S.A.

Endocrinology 147(1):3–8

doi: 10.1210/en.2005-0972

Attenuated Peptide YY Release in Obese Subjects Is Associated with Reduced Satiety

C. W. le Roux, R. L. Batterham, S. J. B. Aylwin, M. Patterson, C. M. Borg, K. J. Wynne, A. Kent, R. P. Vincent, J. Gardiner, M. A. Ghatei, and S. R. Bloom

Departments of Metabolic Medicine (C.W.l.R., M.P., C.M.B., K.J.W., A.K., R.P.V., J.G., M.A.G., S.R.B.), Hammersmith Hospital, Imperial College London, London W12 0NN, United Kingdom; Department of Endocrinology (R.L.B.), University College London, London WC1E 6BT, United Kingdom; and Department of Endocrinology (S.J.B.A.), King's College Hospital, London SE5 9RS, United Kingdom

The responses of the gut hormone peptide YY (PYY) to food were investigated in 20 normal-weight and 20 obese humans in response to six test meals of varying calorie content. Human volunteers had a graded rise in plasma PYY ($R^2 = 0.96$; $P < 0.001$) during increasing calorific meals, but the obese subjects had a lower endogenous PYY response at each meal size ($P < 0.05$ at all levels). The ratio of plasma $PYY_{1–36}$ to $PYY_{3–36}$ was similar in normal-weight and obese subjects. The effect on food intake and satiety of graded doses of exogenous $PYY_{3–36}$ was also evaluated in 12 human volunteers. Stepwise increasing doses of exogenous $PYY_{3–36}$ in humans caused a graded reduction in food intake ($R^2 = 0.38$; $P < 0.001$). In high-fat-fed (HF) mice that became obese and low-fat-fed mice that remained normal weight, we measured plasma PYY, tissue PYY, and PYY mRNA levels and assessed the effect of exogenous administered $PYY_{3–36}$ on food intake in HF mice. HF mice remained sensitive to the anorectic effects of exogenous ip $PYY_{3–36}$. Compared with low-fat-fed fed mice, the HF mice had lower endogenous plasma PYY and higher tissue PYY but similar PYY mRNA levels, suggesting a possible reduction of PYY release. Thus, fasting and postprandial endogenous plasma PYY levels were attenuated in obese humans and rodents. The $PYY_{3–36}$ infusion study showed that the degree of plasma PYY reduction in obese subjects were likely associated with decreased satiety and relatively increased food intake. We conclude that obese subjects have a PYY deficiency that would reduce satiety and could thus reinforce their obesity. (*Endocrinology* 147: 3–8, 2006)

PEPTIDE YY (PYY) is present throughout the intestinal tract, with the highest concentrations in distal segments (1). Two forms are released postprandially: $PYY_{1–36}$ and $PYY_{3–36}$ (1–3). Postprandial plasma PYY concentrations have been reported to be proportional to meal size (1), with levels peaking 2 h after food intake (4, 5). Elevated fasting levels of PYY have been described in several gastrointestinal diseases associated with loss of appetite (6, 7). Batterham *et al.* (4, 5) demonstrated that $PYY_{3–36}$ reduced food intake in both humans and rodents, although a recent publication reported a failure of PYY to inhibit food intake in rodents (8). More recently, however, the effect of PYY as an inhibitor of food intake in rodents has been replicated in a number of studies, and it has become clear that the habituation of laboratory animals to handling and injection is required to demonstrate the effect of $PYY_{3–36}$ (4, 9–14). PYY may thus be an important factor influencing postprandial satiety (15, 16). Fasting endogenous PYY concentrations have been shown to be lower in obese individuals (5). Differences in fasting PYY levels are controversial (17); however, it is apparent that the duration of a fast before a study critically affects plasma PYY concentrations (18). Attenuated postprandial PYY responses in obese subjects have been more consistently reported (5, 17, 19).

First Published Online September 15, 2005

Abbreviations: HF, High-fat-fed; LF, low-fat-fed; PYY, peptide YY; SSC, standard saline citrate; VAS, visual analog scale.

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

In this study, we sought to determine whether obese individuals have lower endogenous PYY levels and whether PYY release could be achieved by sufficient caloric stimulus. We also aimed to determine whether the lower observed postprandial levels of PYY among the obese could be expected to have an effect on food intake. Furthermore, we explored possible mechanisms for the observed relative PYY deficiency among the obese. We thus investigated 1) the endogenous postprandial PYY response, 2) the effect of varied exogenous $PYY_{3–36}$ doses on satiety and food intake, and 3) high-fat-fed (HF) and low-fat-fed (LF) mice for plasma and tissue PYY and PYY mRNA.

Materials and Methods

All human studies were performed according to the principles of the Declaration of Helsinki. The Local Research and Ethics committee at the Hammersmith Hospital approved the postprandial PYY response (03/6499) and multiple PYY infusion (03/6616) studies. Written informed consent was obtained, and exclusion criteria included chronic medical or psychiatric illness, pregnancy, substance abuse, more than two alcoholic drinks per day, and aerobic exercise for more than 30 min three times per week. All animal studies were performed under project licenses issued by the Home Office, United Kingdom (PL/70/5516).

Endogenous postprandial PYY responses

We evaluated the postprandial PYY response to a series of six standard meals in 20 obese and 20 normal-weight subjects (Table 1). The body mass index of all subjects had been stable for 3 months and was 40.3 ± 1.1 kg/m^2 (mean ± SEM) in the obese group and 21.7 ± 0.4 kg/m^2 in the normal-weight group. Both groups consisted of 14 females and six males. The ages were 29.0 ± 2.0 and 28.6 ± 1.6 yr for the obese and normal-weight group, respectively. Subjects attended on three occasions

TABLE 1. Macronutrient content of the standard test meals

	CHD (g)	Fat (g)	Protein (g)	Calories (kcal)
500-ml meals (kcal)				
250	42.3	10.2	16	258
500	52	26.5	18	518
1000	63.3	75.3	17.1	1000
900-ml meals (kcal)				
1000	99	52.9	32.6	1002
2000	107.5	161.7	29.5	2004
3000	94.5	274.95	24.75	2982

Meals consisted of liquid drinks with similar consistency. CHD, Carbohydrate.

after a 12-h overnight fast and received in random order either a 500-ml liquid meal (250, 500, or 1000 kcal) or a 900-ml meal (1000, 2000, or 3000 kcal). All the subjects were required to drink the entire volume, and after consumption of the drink, no liquid was left in the glass. The 1000-kcal meals given as 500 ml or 900 ml allowed investigation of a possible volume effect on plasma PYY response. Visual analog scales (VAS) were completed and venous blood collected every 30 min for 3 h after each meal. Blood samples were centrifuged and plasma was immediately separated and stored at −70 C before analysis. The VAS were used to assess hunger, fullness, and malaise. Subjects indicated their opinion on a 100-mm VAS with text expressing the most positive and most negative ratings anchored at each end (20).

The effect of varied doses of exogenous $PYY_{3–36}$

We used an established protocol (4, 5) to evaluate food intake after iv infusions of human $PYY_{3–36}$ (Bachem, St. Helens, UK) in 12 normal-weight men aged 27.8 ± 3.2 yr with body mass index of 23.2 ± 1.4 kg/m^2. The doses were selected based on previously successful human studies (4, 5). The disappearance half-time on stopping an infusion of PYY has previously been shown to be 9.2 ± 0.4 min, and the volume of distribution was 94 ± 9 ml/kg (21). Subjects were randomized to two subgroups of six. Subjects received four 90-min infusions in a double-blind randomized crossover design. Infusions were separated by a minimum of 4 d. Subgroup A received infusions of saline and 0.2, 0.5, and 0.7 pmol/kg·min $PYY_{3–36}$ and subgroup B received saline and 0.4, 0.6, and 0.8 pmol/kg·min $PYY_{3–36}$. Subjects had a buffet meal 2 h after the termination of the infusion, and calorie intake was calculated. VAS were completed to assess hunger, fullness, and malaise. Venous blood was collected every 30 min during the study and stored at −20 C before analysis in a single assay.

Rodent studies to test possible mechanisms of lower endogenous plasma PYY

Eighty-eight C57B6 mice (Charles River Laboratories, Wilmington, MA) were randomized to 16 wk of diets containing either 2.6% (n = 24) or 60% (n = 64) of calories from fat (Research Diets, New Brunswick, NJ). Using an established protocol, 40 of the HF mice were acclimatized to ip injections (9). Mice were randomly allocated to ip injections with 0.9% saline or 5 μg/100 g $PYY_{3–36}$ (Bachem) after an overnight fast (4). Food intake was measured 1, 2, 4, 8, 12, 24, and 48 h later. The remaining 48 mice were killed after a 12-h fast (n = 24) or 120 min after a 0.5-g high-fat meal (n = 24). A constant section of tissue was dissected from the cecum to the end of the ascending colon in the fasted mice. The tissue was longitudinally separated in equal halves. The samples were weighed and snap frozen in liquid nitrogen.

Peptide extraction and assays for plasma and mRNA

Tissue samples were placed into preheated polypropylene tubes containing 0.5% acetic acid. The wet tissues were weighed at autopsy, and the volume of the acetic acid was adjusted accordingly (10 ml/g). The samples were boiled for 15 min. After another 30 min at room temperature, the supernatant was used to measure PYY immunoreactivity.

All plasma and tissue extracted samples were assayed in duplicate. PYY-like immunoreactivity was measured with a specific and sensitive RIA (5, 22). The assay measured the biologically active components, both the full-length $PYY_{1–36}$ and the fragment $PYY_{3–36}$. The antiserum (Y21) was produced in a rabbit against synthetic porcine PYY (Bachem) coupled to BSA glutaraldehyde and used at a final dilution of 1:50,000. Similar to all current PYY assays, our antibody cross-reacts fully with $PYY_{1–36}$ and $PYY_{3–36}$ but not with pancreatic polypeptide, neuropeptide Y, or any other gastrointestinal hormone. ^{125}I-labeled PYY was prepared by the iodogen method and purified by HPLC. The specific activity of the ^{125}I-labeled PYY was 54 Bq/fmol. The assay was performed in a total volume of 700 μl of 0.06 M phosphate buffer (pH 7.26) containing 0.3% BSA. The samples were incubated for 3 d at 4 C before separation of free and antibody-bound label by sheep antirabbit antibody. Two hundred microliters of unextracted plasma were assayed, whereas 200 μl of PYY-free colloid fluid, Hemacel, was added to standards and other reference tubes to negate any effects of nonspecific assay interference. The assay detected changes of 2 pmol/liter, with intra- and interassay coefficients of variation of 5.8 and 9.8%, respectively.

Before reverse-phase fast protein liquid chromatography, 10 ml of plasma pooled from 10 subjects was pretreated using Sep-Pak C18 cartridges (Waters, Milford, CT) as previously described (23). Recovered plasma samples were resuspended in 0.7 ml water plus trifluoroacetic acid (0.1% vol/vol) and filtered through 0.2-μm hydrophilic membranes (Satorius, Gottingen, Germany). Then, 0.5 ml of the filtrate was fractionated by fast protein liquid chromatography on a high-resolution reverse-phase (Pep RPC HR) C-18 column (Pharmacia, Uppsala, Sweden). The column was eluted with an initial gradient of 0–23.5% (vol/vol) acetonitrile/water/0.1% (vol/vol) trifluoroacetic acid over the first 15 min followed by a gradient of 23.5–24.5% acetonitrile/water/0.1% (vol/vol) trifluoroacetic acid gradient over the next 60 min. The 1.0-ml fractions were collected and dried by vacuum centrifugation (Savant, Greenbush, NY) and reconstituted in assay buffer, and PYY-like immunoreactivity was determined by RIA.

Fasting PYY mRNA levels were measured by Northern blot analysis (n = 6). Total RNA was extracted using Tri-reagent (Helena Biosciences, Sunderland, UK) according to the manufacturer's protocol. A 50-μg amount of total RNA from each tissue was size separated on a denaturing MOPS [3-(*n*-morpholino) propane-sulfonic acid]/formaldehyde gel (1% agarose) and transferred to a Hybond-N membrane (Amersham International, Little Chalfont, UK). The RNA was fixed by baking at 80 C for 2 h before probing with a random primer labeled corresponding to nucleotides 121–450 of rat PYY (accession number M17523). The probe was synthesized using [α-^{32}P]dATP (Amersham) using Klenow DNA polymerase (Promega, Southampton, UK). Hybridization was carried out overnight at 55 C in 5× standard saline citrate (SSC) (1× SSC contains 0.15 M sodium chloride, 15 mM sodium citrate), 5× Denhardt's, 50% (wt/vol) deionized formamide, 100 μg/ml denatured sonicated herring sperm DNA, and 100 μg/ml yeast tRNA. Nonspecific hybridization was removed by increasingly stringent washes, the final one being in 0.1× SSC/0.1% (wt/vol) SDS at 70 C for 30 min.

The Northern blot was exposed to a phosphoimager screen and quantified using ImageQuant 5.2 (Molecular Dynamics, Sunnyvale, CA). The Northern blot was normalized using oligo-dT as a probe (24).

Statistical analysis

Data are expressed as means ± SEM. Values for the area under the curve were calculated with the use of the trapezoidal rule. End points were compared with the use of two-tailed, unpaired Student's *t* tests or ANOVA. For Fig. 1, C and D, the Wilcoxon two-sample test was used. For Fig. 2, one-way ANOVA with 6 degrees of freedom was used with Student-Newman-Keuls method as *post hoc* analysis. For Fig. 3B, one-way ANOVA with Kruskal-Wallis statistic and Dunn's multiple comparison test was used. Correlations were determined by univariate linear regression (GraphPad Prism).

Results

Endogenous postprandial PYY responses

In the postprandial PYY study, obese volunteers had a significantly lower fasting PYY (7.1 ± 1.3 pmol/liter) than the normal-weight subjects (9.3 ± 0.6 pmol/liter; $P < 0.001$). Plasma PYY peaked 90 min after the meal was ingested. A graded rise in peak plasma PYY was observed for both nor-

mal-weight ($R^2 = 0.96$; $P < 0.001$) and obese ($R^2 = 0.95$; $P < 0.001$) subjects in response to increasing calorific meals. The ratio of $PYY_{3–36}$ to $PYY_{1–36}$ for peak levels occurring at 90 min after a 2000-kcal meal was 3.6 in the normal-weight and 3.4 in the obese subjects (Fig. 1, A and B). Obese subjects, however, had a lower peak PYY response than normal-weight subjects for each calorie load (Fig. 1C) ($P < 0.05$ for all meals). Thus, approximately double the meal calorie content was required to achieve equivalent PYY levels to those observed in normal-weight subjects. Moreover, this lower PYY level in the obese subjects was matched by a lower level of fullness after the 1000-, 2000-, and 3000-kcal meals as measured by VAS. The difference was significant at 30 min ($P < 0.05$) and was sustained until 180 min ($P < 0.01$) postprandially. PYY has been proposed as an intermediate meal regulator, and hence the data in Fig. 1D is shown for 3 h after the meal was consumed. The PYY response after 1000 kcal was not significantly different in the 500- and 900-ml protocols, evidence against a significant effect of volume on PYY response (Fig. 1C). There was no difference between the VAS scores for hunger or malaise between the normal-weight and obese groups at any time during the study.

The effect of varied doses of exogenous $PYY_{3–36}$

In the human multiple-dose infusion study there was a strong correlation between infused $PYY_{3–36}$ doses and measured plasma PYY levels ($R^2 = 0.73$; $P < 0.001$) (Fig. 2A). No difference in VAS-rated malaise, desire to eat, or hunger was detected when the meal was served ($P > 0.1$). There was a strong negative correlation between infused doses of $PYY_{3–36}$ and food intake ($R^2 = 0.3$; $P < 0.001$) with a significant reduction in calorie intake observed at doses of 0.7 and 0.8 pmol/kg·min (Fig. 2B). In contrast to the graded reduction in calorie intake across the infusion doses, a significant rise in fullness scores was observed with an apparent threshold at an infusion dose of 0.5 pmol/kg·min, corresponding to a plasma PYY level of 40 pmol/liter (Fig. 2C). Moreover, no additional increase in fullness scores was observed with $PYY_{3–36}$ doses above 0.5 pmol/kg·min.

Rodent studies to test possible mechanisms of lower endogenous plasma PYY

The 64 mice fed the high-fat diet (HF) weighed significantly more than the 24 fed a low-fat diet (LF) (42.6 ± 1.3 g

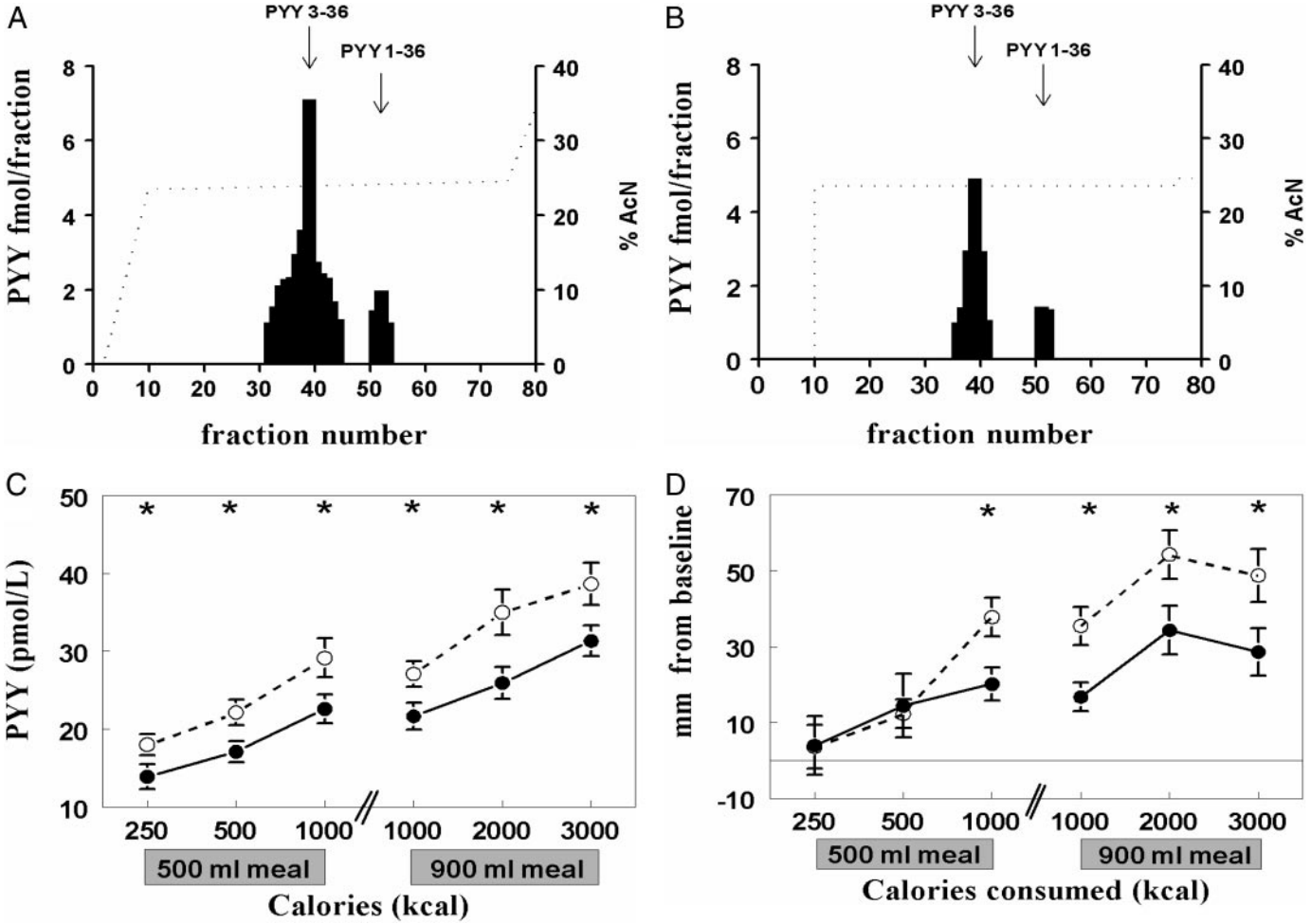

FIG. 1. A and B, Isoforms $PYY_{1–36}$ and $PYY_{3–36}$ in normal-weight (A) and obese (B) patients 90 min after a 2000-kcal meal; C, peak PYY levels in obese (●) and normal-weight (○) subjects at 90 min after the meal; D, fullness scores at 180 min after the meal, measured by VAS in the obese (●) and normal-weight (○) subjects. *, $P < 0.05$ (unpaired t test).

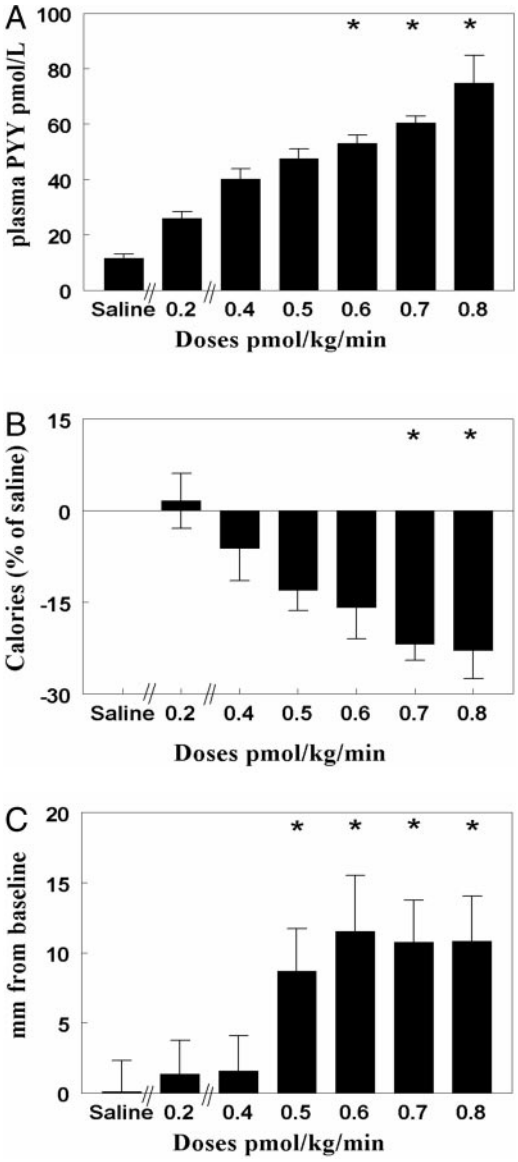

FIG. 2. A, PYY levels achieved after infusion of increasing doses in normal-weight subjects; B, effect for each infusion rate of $PYY_{3–36}$ on calories consumed when normalized for consumption on saline infusion day; C, VAS shows change (in millimeters) in level of fullness at end of the infusion. *, $P < 0.05$ compared with saline (one-way ANOVA).

for HF *vs.* 30.1 ± 0.8 g for LF; $P < 0.001$). The ip administration of $PYY_{3–36}$ to 40 HF mice resulted in a reduced food intake for up to 8 h (Fig. 3A) compared with saline controls. The group of HF mice (n = 24) had lower plasma PYY levels than the group of LF mice (n = 24), both fasting (35.7 ± 3.8 pmol/liter for HF *vs.* 47.2 ± 3.1 pmol/liter for LF; $P = 0.048$) and postprandially (46.3 ± 2.9 pmol/liter for HF *vs.* 56.6 ± 4.2 pmol/liter for LF; $P = 0.03$) (Fig. 3B). The tissue PYY levels in the ascending colon were higher in the HF mice (340.2 ± 56 pmol/g for HF *vs.* 148.0 ± 23 pmol/g for LF; $P < 0.05$; n = 24) (Fig. 3C). PYY mRNA levels in the ascending colon, however, was similar between the two groups (Fig. 3D).

Discussion

Termination of a meal depends on the balance between hunger before and fullness or satiety subsequent to the consumption of food (25, 26). A number of hormonal signals, including PYY, are generated during a meal, and it has been suggested that several of these signals may contribute to satiety (15). The etiology of obesity is still unclear, but it has been suggested that decreased satiety is one factor in its initiation and maintenance. For example, it has been reported that overweight and obese individuals required approximately 225 kcal more than normal-weight individuals to reach maximum satiety (27), whereas as little as 100 kcal in excess of daily requirements is enough to lead to weight gain (28). Obese subjects have delayed onset of satiety after consuming an *ad libitum* meal, and it has been speculated that this is related to alterations in hormone responses to food intake (27). We therefore investigated whether there are abnormalities in the PYY system at the level of synthesis, secretion, or sensitivity. The study reported here suggests that the contribution of $PYY_{1–36}$ and $PYY_{3–36}$ is similar in lean and obese subjects. The study supports the previous finding that obese subjects have reduced plasma PYY levels (5, 17, 19). In addition, we found that obese subjects have an attenuated PYY response across a range of meals with different calorie content. Greater meal calorie content was required to increase plasma PYY concentrations in obese to similar levels seen in normal-weight subjects. Infusions of exogenous $PYY_{3–36}$ at increasing doses produced an increased fullness and decreased food intake in normal-weight individuals. Taken together, these findings suggest that lower endogenous postprandial PYY levels may relate to reduced satiety and that obese subjects may have a weaker PYY-induced satiety signal for an equivalent meal.

Similar to human subjects (5), HF mice remain sensitive to the anorectic effects of exogenous $PYY_{3–36}$. In HF mice, the reduced plasma PYY levels were associated with elevated colon PYY levels, whereas the PYY mRNA levels were similar in the LF and HF groups. Our findings are consistent with a report in HF mice of reduced plasma levels and increased tissue levels for another L-cell-produced hormone, glucagon-like peptide 1 (29). These findings suggest that the plasma PYY deficiency may result from impaired PYY release rather than decreased synthesis, although we cannot exclude the possibility of an enhanced clearance rate or reduction in mRNA translation. PYY cell density was not measured in our study but may be important in future work to evaluate the discrepancy between low plasma levels and high tissue levels.

Obesity does not seem to cause a peripheral resistance to PYY, unlike the marked resistance observed for leptin and insulin (30, 31). The HF mice appear to be sensitive to the effects of $PYY_{3–36}$. This is consistent with previous reports (13) and the sensitivity to $PYY_{3–36}$ observed in obese humans (5). The definitive role of PYY in the pathogenesis of obesity and the mechanisms that contribute to the reduced plasma levels of PYY in obese humans and rodents remains to be determined. Models with genetic mutations may prove helpful in future as was recently shown when a mutation in PYY was demonstrated to be associated with the development of

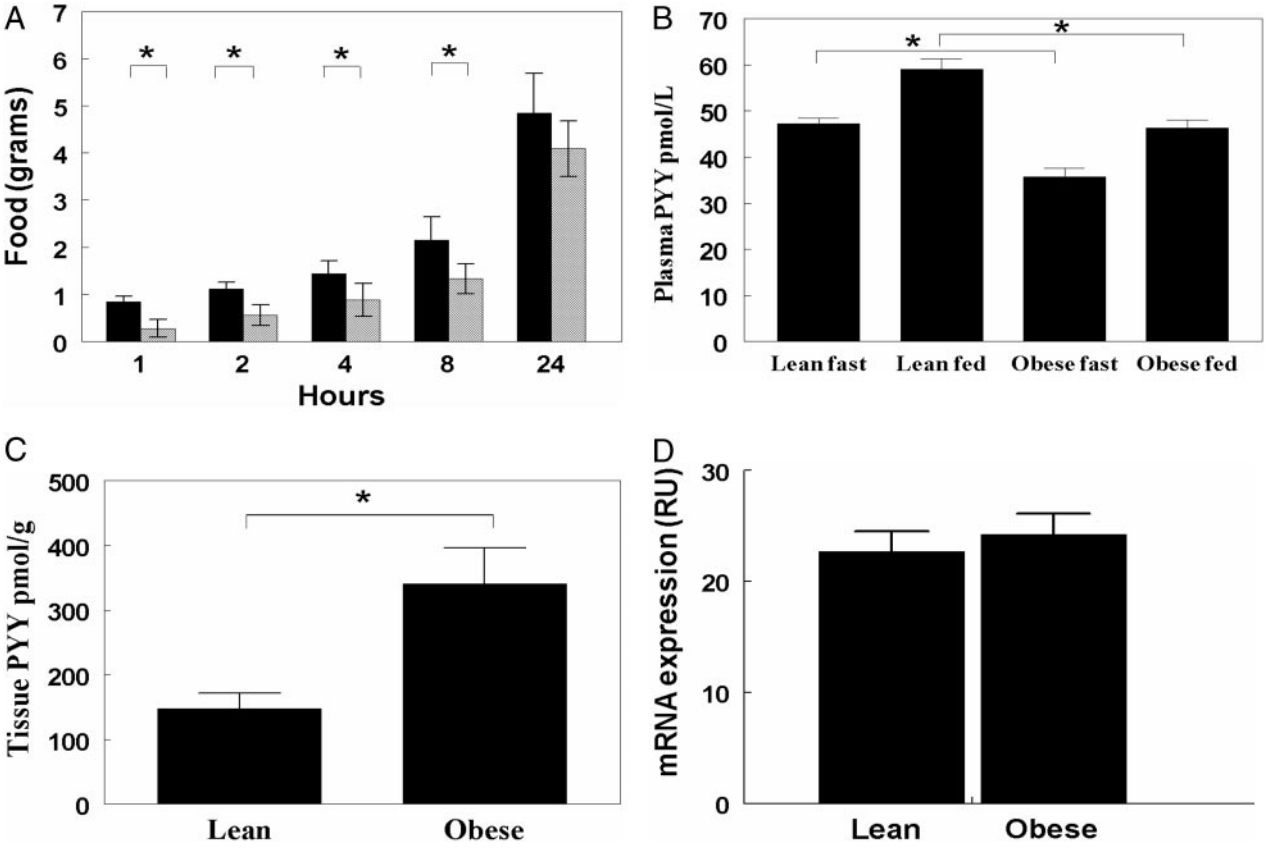

FIG. 3. A, Food intake at 1, 2, 4, 8, and 24 h in diet-induced obese mice after ip $PYY_{3–36}$ (*striped bars*) compared with saline (*solid bars*); B, plasma PYY fasting and after 0.5 g chow in normal-weight and obese mice; C, ascending colon tissue levels of PYY in obese and normal-weight mice; D, mRNA levels from ascending colon tissue in normal-weight (N) and obese (O) mice. *, $P < 0.05$ (*t* test between groups indicated by *lines*).

type 2 diabetes mellitus (32). Our study also addresses the question as to whether low plasma PYY is a cause or consequence of obesity. We observed that after randomization of mice into HF or LF groups, plasma PYY was lower in the diet-induced obese mice. We would therefore conclude that low plasma PYY is more likely to be a consequence rather than a cause of obesity. The apparent reduction in PYY release may have a potential maintenance effect rather than a causative effect on obesity.

Taken together, these studies suggest that the observed lower postprandial PYY levels in obese individuals may result in an increase in food intake to achieve the same level of satiety as seen in normal-weight subjects. PYY release from the intestinal tract may be inhibited in the obese, thus leaving obese subjects with a functional deficiency in PYY-induced satiety. Low plasma PYY may therefore reinforce obesity.

Acknowledgments

Received August 1, 2005. Accepted September 10, 2005.

Address all correspondence and requests for reprints to: Prof. S. R. Bloom, Department of Metabolic Medicine, 6th Floor Commonwealth Building, Hammersmith Hospital, Imperial College London, London W12 0NN, United Kingdom. E-mail: s.bloom@imperial.ac.uk.

C.L.R. and K.J.W. are supported by a Wellcome Clinical Fellowship, R.L.B. by a Medical Research Council Intermediate Fellowship. The research was supported by EU FP6 funding (contract no. LSHM-CT-2003-503041). This publication reflects the authors' views and not necessarily those of the European Union. The information in this document is provided as is, and no guarantee or warranty is given that the information is fit for any particular purpose. The user thereof uses the information at its sole risk and liability.

References

1. **Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR** 1985 Human distribution and release of a putative new gut hormone, peptide YY. Gastroenterology 89:1070–1077
2. **Eberlein GA, Eysselein VE, Schaeffer M, Layer P, Grandt D, Goebell H, Niebel W, Davis M, Lee TD, Shively JE** 989 A new molecular form of PYY: structural characterization of human PYY(3–36) and PYY(1–36). Peptides 10: 797–803
3. **Grandt D, Schimiczek M, Beglinger C, Layer P, Goebell H, Eysselein VE, Reeve Jr JR** 1994 Two molecular forms of peptide YY (PYY) are abundant in human blood: characterization of a radioimmunoassay recognizing PYY 1–36 and PYY 3–36. Regul Pept 51:151–159
4. **Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR** 2002 Gut hormone PYY(3–36) physiologically inhibits food intake. Nature 418:650–654
5. **Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, Bloom SR** 2003 Inhibition of food intake in obese subjects by peptide YY3–36. N Engl J Med 349:941–948
6. **Adrian TE, Savage AP, Fuessl HS, Wolfe K, Besterman HS, Bloom SR** 1987 Release of peptide YY (PYY) after resection of small bowel, colon, or pancreas in man. Surgery 101:715–719
7. **Adrian TE, Savage AP, Bacarese-Hamilton AJ, Wolfe K, Besterman HS, Bloom SR** 1986 Peptide YY abnormalities in gastrointestinal diseases. Gastroenterology 90:379–384
8. **Tschop M, Castaneda TR, Joost HG, Thone-Reineke C, Ortmann S, Klaus S, Hagan MM, Chandler PC, Oswald KD, Benoit SC, Seeley RJ, Kinzig KP, Moran TH, Beck-sickinger AG, Koglin N, Rodgers RJ, Blundell JE, Ishii Y, Beattie AH, Holch P, Allison DB, Raun K, Madsen K, Wulff BS, Stidsen CE, Birringer M, Kreuzer OJ, Schindler M, Arndt K, Rudolf K, Mark M, Deng**

XY, Withcomb DC, Halem H, Taylor J, Dong J, Datta R, Culler M, Craney S, Flora D, Smiley D, Heiman ML 2004 Physiology: does gut hormone PYY3–36 decrease food intake in rodents? Nature 430:1

9. **Halatchev IG, Ellacott KL, Fan W, Cone RD** 2004 Peptide YY3–36 inhibits food intake in mice through a melanocortin-4 receptor-independent mechanism. Endocrinology 145:2585–2590
10. **Challis BG, Coll AP, Yeo GS, Pinnock SB, Dickson SL, Thresher RR, Dixon J, Zahn D, Rochford JJ, White A, Oliver RL, Millington G, Aparicio SA, Colledge WH, Russ AP, Carlton MB, O'Rahilly S** 2004 Mice lacking pro-opiomelanocortin are sensitive to high-fat feeding but respond normally to the acute anorectic effects of peptide-YY3–36. Proc Natl Acad Sci USA 101:4695–4700
11. **Cox JE, Randich A** 2004 Enhancement of feeding suppression by PYY(3–36) in rats with area postrema ablations. Peptides 25:985–989
12. **Riediger T, Bothe C, Becskei C, Lutz TA** 2004 Peptide YY directly inhibits ghrelin-activated neurons of the arcuate nucleus and reverses fasting-induced c-Fos expression. Neuroendocrinology 79:317–326
13. **Pittner RA, Moore CX, Bhavsar SP, Gedulin BR, Smith PA, Jodka CM, Parkes DG, Paterniti JR, Srivastava VP, Young AA** 2004 Effects of PYY[3–36] in rodent models of diabetes and obesity. Int J Obes Relat Metab Disord
14. **Chelikani PK, Haver AC, Reidelberger RD** 2005 Intravenous infusion of peptide YY(3–36) potently inhibits food intake in rats. Endocrinology 146: 879–888
15. **Schwartz MW, Morton GJ** 2002 Obesity: keeping hunger at bay. Nature 418:595–597
16. **Saper CB, Chou TC, Elmquist JK** 2002 The need to feed: homeostatic and hedonic control of eating. Neuron 36:199–211
17. **Stock S, Leichner P, Wong AC, Ghatei MA, Kieffer TJ, Bloom SR, Chanoine JP** 2005 Ghrelin, peptide YY, glucose-dependent insulinotropic polypeptide, and hunger responses to a mixed meal in anorexic, obese, and control female adolescents. J Clin Endocrinol Metab 2005 90:2161–2168
18. **Tovar SA, Seoane LM, Caminos JE, Nogueiras R, Casanueva FF, Dieguez C** 2004 Regulation of peptide YY levels by age, hormonal, and nutritional status. Obes Res 12:1944–1950
19. **Korner J, Bessler M, Cirilo LJ, Conwell IM, Daud A, Restuccia NL, Wardlaw SL** 2005 Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. J Clin Endocrinol Metab 90:359–365
20. **Raben A, Tagliabue A, Astrup A** 1995 The reproducibility of subjective appetite scores. Br J Nutr 73:517–530
21. **Adrian TE, Sagor GR, Savage AP, Bacarese-Hamilton AJ, Hall GM, Bloom SR** 1986 Peptide YY kinetics and effects on blood pressure and circulating pancreatic and gastrointestinal hormones and metabolites in man. J Clin Endocrinol Metab 63:803–807
22. **Savage AP, Adrian TE, Carolan G, Chatterjee VK, Bloom SR** 1987 Effects of peptide YY (PYY) on mouth to caecum intestinal transit time and on the rate of gastric emptying in healthy volunteers. Gut 28:166–170
23. **Patterson M, Murphy KG, Le Roux CW, Ghatei MA, Bloom SR** 2005 Characterization of ghrelin-like immunoreactivity in human plasma. J Clin Endocrinol Metab 90:2205–2211
24. **Harley CB** 1988 Normalization of RNA dot blots with oligo(dT). Trends Genet 4:152
25. **Nicolaidis S, Even P** 1985 Physiological determinant of hunger, satiation, and satiety. Am J Clin Nutr 42:1083–1092
26. **Geiselman PJ** 1996 Control of food intake. A physiologically complex, motivated behavioral system. Endocrinol Metab Clin North Am 25:815–829
27. **Delgado-Aros S, Cremonini F, Castillo JE, Chial HJ, Burton DD, Ferber I, Camilleri M** 2004 Independent influences of body mass and gastric volumes on satiation in humans. Gastroenterology 126:432–440
28. **Hill JO, Wyatt HR, Reed GW, Peters JC** 2003 Obesity and the environment: where do we go from here? Science 299:853–855
29. **Anini Y, Brubaker PL** 2003 Role of leptin in the regulation of glucagon-like peptide-1 secretion. Diabetes 52:252–259
30. **West TE, Owens D, Sonksen PH, Srivastava MC, Tompkins CV, Nabarro JD** 1975 Metabolic responses to monocomponent human insulin infusions in normal subjects and patients with liver and endocrine disease. Clin Endocrinol (Oxf) 4:573–584
31. **Hukshorn CJ, Saris WH, Westerterp-Plantenga MS, Farid AR, Smith FJ, Campfield LA** 2000 Weekly subcutaneous pegylated recombinant native human leptin (PEG-OB) administration in obese men. J Clin Endocrinol Metab 85:4003–4009
32. **Torekov SS, Larsen LH, Glumer C, Borch-Johnsen K, Jorgensen T, Holst JJ, Madsen OD, Hansen T, Pedersen O** 2005 Evidence of an association between the Arg72 allele of the peptide YY and increased risk of type 2 diabetes. Diabetes 54:2261–2265

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