Pancreatic Polypeptide Is Involved in the Regulation of Body Weight in Pima Indian Male Subjects

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Pancreatic polypeptide (PP) is released from the pancreas in response to a meal. In humans, low-circulating PP levels have been observed in obesity, and administration of pharmacological doses of PP has been shown to decrease food intake. The aim of the present study was to investigate whether low circulating PP is associated with weight gain in Pima Indians. Plasma PP concentrations were measured after an overnight fast and 30 min after a standardized mixed meal in 33 nondiabetic male subjects who had a follow-up visit 4.9 ± 2.5 years later. Cross-sectionally, fasting and postprandial PP levels were negatively associated with body size and adiposity. Prospectively, the change in PP response to the meal was negatively associated with the change in body weight ($r = -0.53$, $P = 0.002$). In contrast, a high fasting PP level was positively associated with change in body weight ($r = 0.45$, $P = 0.009$). In conclusion, our results provide evidence that, even within the physiological range, PP contributes to the regulation of energy balance in humans. However this contribution appears to be more complex than anticipated because of the opposite effect of fasting and postprandial PP on the risk of future weight gain. *Diabetes* 53:3091–3096, 2004

Pancreatic polypeptide (PP) is a 36–amino acid peptide produced by the F-cells of the pancreas. After ingestion of a meal, PP is released rapidly into the circulation, where levels remain elevated for several hours (1). In the brain, PP exerts a predominantly orexigenic effect when administered directly (2). In the gastrointestinal tract, PP inhibits gastric emptying rate, exocrine pancreatic secretion, and gallbladder motility (3), and in contrast to its central effects, intraperitoneal administration of PP decreases food intake and increases energy expenditure (2). Repeated administration of PP to obesity-prone animals suppressed excessive weight gain (4), and mice who overexpress PP in the pancreas because of genetic manipulation are characterized by decreased food intake and lower body weight (5).

Altered PP secretion has been reported in clinical syndromes associated with abnormal eating behavior in humans. Subjects with Prader-Willi syndrome, a genetic form of obesity characterized by extreme hyperphagia, have a diminished PP response to a meal (6). Decreased postprandial secretion of PP has also been observed in individuals with morbid obesity (7), whereas subjects with anorexia nervosa are characterized by an exaggerated postprandial release of PP (8,9). Exogenous administration of PP was followed by decreased food intake in Prader-Willi syndrome (10) and in healthy individuals (11), suggesting that increasing PP pharmacologically may represent a therapeutic option for the treatment of obesity (12).

Surprisingly, the Pima Indians of Arizona, a population with excessive weight gain beginning at a very early age (13,14), are characterized by elevated circulating PP. This is true for children, who have higher fasting plasma PP concentrations than their age- and sex-matched Caucasian counterparts (15), and in adults, who have elevated fasting concentrations and enhanced postprandial secretion of PP (15–17). Although these observations seem to be inconsistent with a proposed anorexigenic effect of PP, their cross-sectional nature does not establish whether abnormal PP secretion is involved in the etiology of obesity in this population. Because prospective studies are better suited to identifying risk factors for the development of a disease, we have examined the effect of fasting and postprandial PP levels on prospective changes in body weight in nondiabetic Pima Indians. We hypothesized that increased fasting and postprandial PP secretion would be associated with a decreased risk of weight gain.

RESEARCH DESIGN AND METHODS

The individuals in this study were part of a larger study in which the cross-sectional relationship between PP and insulin was previously described (15). A total of 33 Pima Indian male subjects from the original cohort had a follow-up visit for the measurement of body weight and glucose tolerance and were included in this analysis.

At baseline, all subjects were between 18 and 50 years of age and normal glucose tolerant according to an oral glucose tolerance test (OGTT; World Health Organization 1999 criteria) (18). The subjects were nonsmokers and, except for obesity, healthy according to a physical examination and routine laboratory tests. For the baseline visit, all subjects were admitted for 8–10 days to the National Institutes of Health Clinical Research Unit in Phoenix, Arizona. On admission, they were fed a weight-maintaining diet (50, 30, and 20% of daily calories provided as carbohydrate, fat, and protein, respectively) and abstained from strenuous exercise. Height and weight were measured with subjects wearing a preweighed hospital gown and without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters. Percentage of body fat (% body fat) was assessed by underwater weighing, with determination of residual lung volume by helium dilution (19), or by dual-energy X-ray absorptiometry (DPX-L; Lunar, Madison, WI), using a conversion equation to make measurements comparable between the methods (20). At least 3 days after admission and after a 12-h overnight fast, all subjects underwent a 2-h 75-g OGTT. Plasma glucose concentrations were

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OGTT, oral glucose tolerance test; PP, pancreatic polypeptide.

TABLE 1
Anthropometric and metabolic measurements at baseline and follow-up and their change from baseline to follow-up ($n = 33$)

	Baseline	Follow-up	Change	P for change
Age (years)	27 ± 6	32 ± 7	5 (0.9–9.4)	—
Body weight (kg)	94 ± 20	100 ± 21	6 (−7 to 26)	<0.001
BMI (kg/m^2)	32 ± 6	34 ± 6	2 (−6 to 9)	0.007
Waist circumference (cm)	105 ± 15	112 ± 14	6 (−5 to 18)	<0.001
Percent body fat	27 ± 6	—	—	—
Fasting glucose (mg/dl)	83 ± 9	89 ± 13	6 (−26 to 21)	0.004
2-h glucose (mg/dl)	104 ± 21	117 ± 28	13 (−41 to 62)	0.007
$PP_{fasting}$ (pmol/l)	37 ± 23	—	—	—
PP_{meal} (pmol/l)	114 ± 79	—	—	—

Data are means ± SD or mean (range).

determined by the glucose-oxidase method (Beckman Instruments, Fullerton, CA).

At the baseline visit, subjects underwent a standardized mixed meal test as previously described (21). In brief, at 7:00 A.M., after a 12-h overnight fast, an intravenous catheter was placed in an antecubital vein for blood sampling and kept patent with a 0.9% saline infusion. Subjects rested quietly in bed throughout the test. At 8:00 A.M., after two baseline blood samples were drawn at −15 and 0 min, subjects consumed a standard test meal (toast, butter, jelly, scrambled eggs, and orange juice) containing ~20% of their estimated 24-h sedentary energy expenditure distributed as 40, 44, and 16% of calories from carbohydrate, fat, and protein, respectively. All subjects finished the meal within 15 min. A postprandial blood sample was drawn at 30 min. All blood samples were drawn with prechilled syringes, transferred into prechilled tubes, and immediately placed on ice. All tubes were cold-centrifuged (4°C) within minutes of collection, and the plasma aliquots were kept frozen until assayed. Plasma PP concentrations were measured by radioimmunoassay in the −15- and 30-min plasma samples (intra-assay variation 2.2%; Alpco, Windham, NH).

At the follow-up visit, subjects were admitted to the clinical research unit as described above ($n = 27$) or were studied as outpatients after an overnight fast ($n = 6$). All subjects underwent a physical examination, which included height, weight, and waist and thigh circumference measurements, and a 75-g OGTT. The subjects who were diabetic at follow-up, according to World Health Organization criteria (18), were excluded from the prospective analyses.

The protocol was approved by the tribal council of the Gila River Indian Community and by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases. All subjects provided written informed consent before participation.

Statistical analyses. Statistical analyses were performed using the procedures of the SAS Institute (Cary, N.C.). Results are presented as means ± SD. Postprandial PP response was expressed as postprandial concentration of PP (at 30 min) and as absolute and relative change from fasting level. Absolute change was calculated as the difference between the postprandial and fasting levels whereas relative changes were calculated as absolute change divided by fasting levels and expressed as a percentage. To approximate a normal distribution, PP concentrations were logarithmically transformed before statistical analysis.

In the cross-sectional analyses, relationships between PP levels and body weight, BMI, percent body fat, and fasting and 2-h plasma glucose were examined by calculating Pearson correlation coefficients.

Prospective changes in body weight and waist circumference were calculated as the absolute (follow-up minus baseline) and relative (follow-up minus baseline divided by baseline) differences between follow-up and baseline measurements. Pearson correlation coefficients were then calculated to estimate the correlation of fasting and postprandial concentrations of PP with changes in body weight and waist circumference. General linear regression models were also used to evaluate the effect of PP concentrations on body weight and waist circumference at follow-up adjusted for baseline body weight and/or waist circumference, age and time of follow-up. Models including waist circumference were additionally adjusted for changes in body weight. Differences in anthropometric and metabolic measurements between the two visits were assessed by paired Student's t test.

RESULTS

The anthropometric and metabolic characteristics at baseline and follow-up of the 33 subjects selected for this study are summarized in Table 1. In cross-sectional analyses, we found negative relationships between fasting PP concentrations and absolute and relative postprandial changes in PP concentration ($r = -0.35$, $P = 0.05$ and $r = -0.65$, $P < 0.0001$; respectively). Fasting and postprandial PP concentrations were negatively associated with BMI, body weight, percent body fat, and waist circumference, although not all of the relationships reached a level of statistical significance (Fig. 1). Absolute and relative postprandial changes in PP concentrations were not associated with any of the baseline anthropometric measures ($P > 0.5$ for all). Neither fasting nor postprandial plasma PP concentrations were associated with age and fasting or 2-h plasma glucose concentrations from the OGTT.

Prospectively, the study group, on average, gained weight, increased their waist circumference, and worsened their glucose tolerance (Table 1). In simple correlation analyses, fasting PP concentrations were positively associated, whereas postprandial increments of plasma PP were negatively associated, with changes in body weight (Table 2). After adjustment for baseline weight, age, and time of follow-up using multiple regression analysis, fasting concentrations of PP were a significant determinant of body weight at follow-up; in contrast, only a trend was observed for the effect of postprandial PP concentrations (Fig. 2).

In simple correlation analyses, fasting PP concentrations were positively associated, whereas postprandial changes in PP concentrations were negatively associated with changes in waist circumference (Table 2). After adjustment for waist circumference at baseline, change in body weight, age, and time of follow-up using multiple regression analysis, postprandial but not fasting PP concentrations were a significant determinant of waist circumference at follow-up (Fig. 1). Neither fasting nor postprandial PP concentrations were associated with changes in fasting and 2-h OGTT plasma glucose concentrations ($P > 0.3$, all) (data not shown).

DISCUSSION

In the present study, we observed a negative cross-sectional association between fasting and postprandial concentrations of PP and adiposity in Pima Indian male subjects. Consistent with the hypothesis that PP is an anorexigenic hormone, we have shown that an elevated early postprandial PP response is associated with a decreased risk of weight gain. Surprisingly, however, we also found that a high fasting plasma PP concentration is associated with a greater risk of weight gain.

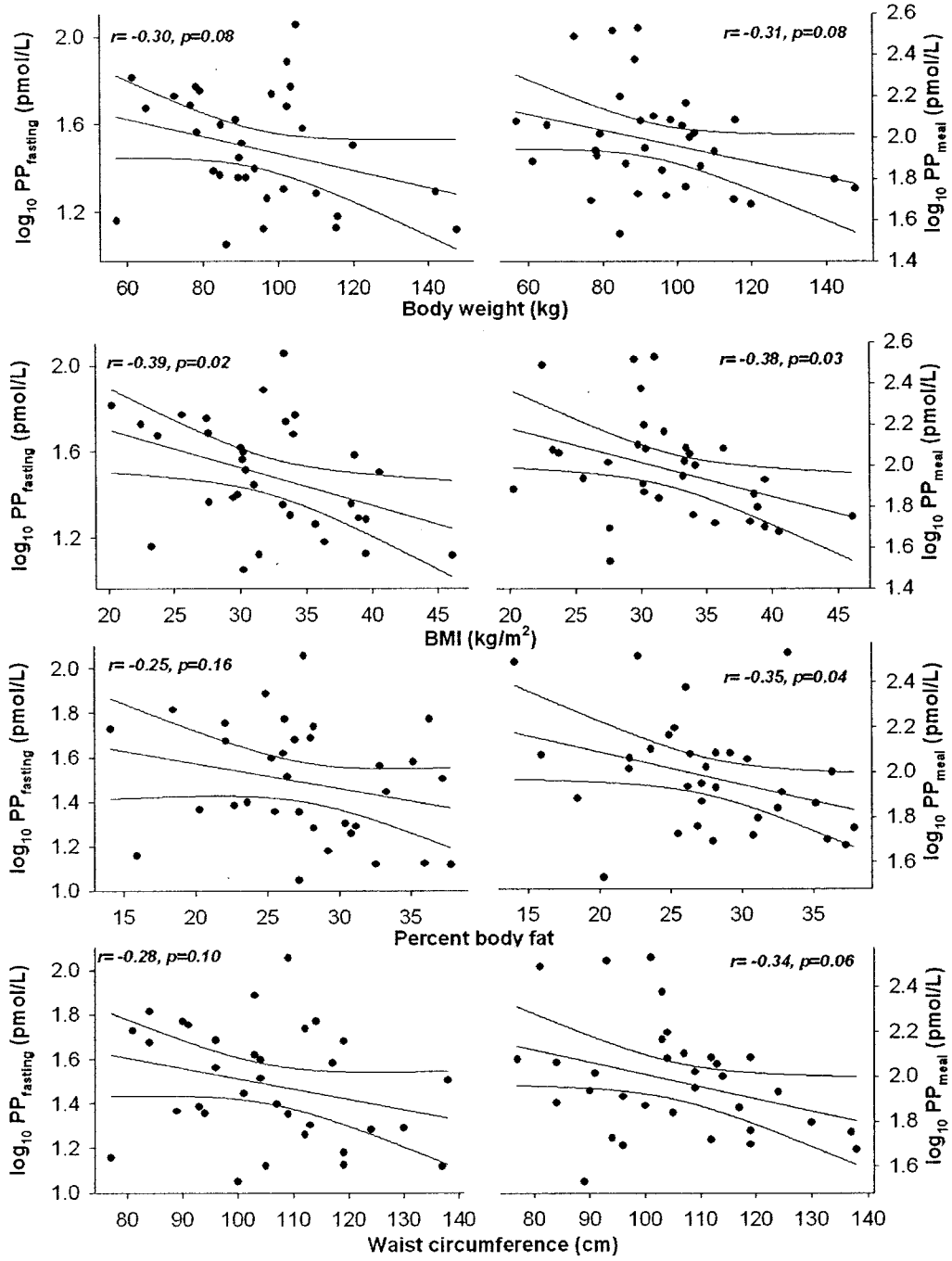


FIG. 1. Cross-sectional relationship between fasting and postprandial levels of PP and anthropometric measures in 33 normal glucose tolerant Pima Indian male subjects.

The results of the present study indicate that, similar to other populations (7), fasting and postprandial PP secretion in Pima Indian male subjects is negatively associated with obesity. Our prospective analyses also show that greater PP secretion after ingestion of a meal is associated with reduced weight gain. In human studies, decreased appetite and food intake were found after acute administration of pharmacological doses of PP (10,11). Our results are consistent with studies in mice showing reduced food intake and lower body weight gain after peripheral administration of PP at doses that increased plasma levels in a manner similar to meal ingestion (2,22).

Several physiological mechanisms could explain the anorexigenic effect of postprandial PP release. Rapid gastric emptying rate has been described in obesity (23), and administration of PP to mice is followed by inhibition of gastric emptying (22). However, in humans, PP had no effect on the gastric emptying rate in a study involving five subjects (24); moreover, the decrease in hunger after PP administration was shown to precede meal ingestion, suggesting that at least part of the anorexigenic effect of PP may not involve changes in gastric emptying (11).

Because intracerebroventricular administration of PP has orexigenic effects (2), peripheral pathways are thought to mediate the anorexigenic effects of PP. Resection of the hepatic vagal nerves abolishes the anorexigenic effect of

TABLE 2
Pearson correlation coefficients between fasting PP levels and PP response to meal and changes in body weight, waist circumference, and fasting and 2-h OGTT plasma glucose levels over 5 years (average [range 0.9–9.4]) of follow-up in 33 nondiabetic Pima Indian male subjects

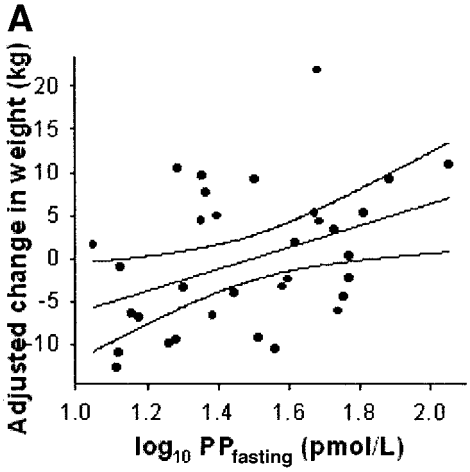
Variable	Log_{10} $PP_{fasting}$ (pmol/l)	Log_{10} PP_{meal} (pmol/l)	Log_{10} ΔPP (pmol/l)	Log_{10} ΔPP (%)
ΔBody weight				
kg	0.42*	−0.19	−0.45†	−0.51†
%	0.47†	−0.17	−0.45†	−0.53†
kg per year	0.40‡	−0.19	−0.41‡	−0.47†
% per year	0.42‡	−0.17	−0.40‡	−0.48†
ΔWaist circumference				
cm	0.37‡	−0.20	−0.32	−0.40‡
%	0.37‡	−0.18	−0.30	−0.38‡
cm per year	0.34*	−0.21	−0.34*	−0.40‡
% per year	0.34*	−0.20	−0.34*	−0.40‡

*$P < 0.07$; †$P < 0.01$; ‡$P < 0.05$; ΔPP (pmol/l) = $PP_{meal} - PP_{fasting}$; ΔPP (%) = 100 × ΔPP (pmol/l)/$PP_{fasting}$.

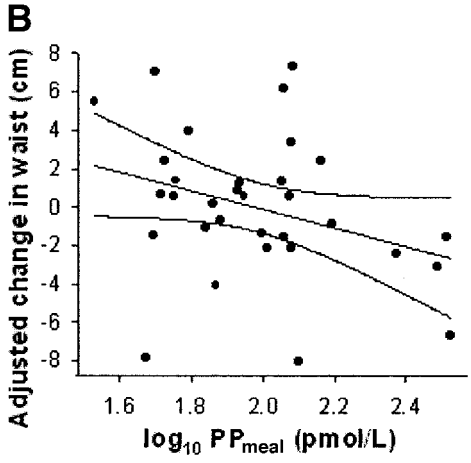
PP in mice (4). It has been also observed that hepatic vagotomy eliminates PP-induced sympathetic activation of the visceral adipose tissue and adrenal glands (4). Because abdominal fat is characterized by more dense sympathetic innervations than other fat depots (rev. in 25), changes in sympathetic activity, which has mainly lipolytic effects, may explain the negative association between postprandial PP levels and abdominal fat accumulation in our study.

Although mounting evidence suggests that PP is an anorexigenic hormone (4,11,22), previous studies in Pima Indians, a population that is very prone to obesity, have led to the unexpected finding of increased fasting levels and enhanced postmeal secretion of PP in this population compared with Caucasians (15–17). Here we show that, also unexpectedly, high levels of PP under fasting conditions were associated with increased weight gain. Although these results are difficult to reconcile with the established anorexigenic effects of PP, we offer a few possible interpretations of the findings.

The positive relationship between fasting PP levels and weight gain may simply be a type 1 statistical error. Nevertheless, although the number of subjects involved in our prospective analyses was indeed small, it is worth



Dependent: weight at follow-up R^2=0.90			
Independent	β	S.E.	P
Intercept	-3.0	17	0.9
Age	0.2	0.2	0.3
Weight at baseline	1.0	0.07	<0.001
Time of follow-up	-0.6	0.6	0.4
$PP_{fasting}$	16	6	0.009
PP_{meal}	-10	6	0.1



Dependent: waist at follow-up R^2=0.94			
Independent	β	S.E.	P
Intercept	28	10	0.01
Age	0.02	0.1	0.9
Waist at baseline	0.9	0.05	<0.001
Change in weight	0.5	0.1	<0.001
Time of follow-up	0. 6	0.3	0.09
$PP_{fasting}$	0.6	3	0.9
PP_{meal}	-7	3	0.05

FIG. 2. Multivariate relationships between fasting plasma PP at baseline (*A*) and change in body weight (*B*), postprandial plasma PP at baseline, and change in waist circumference in 33 nondiabetic Pima Indian male subjects.

noting the consistency of the association over different statistical models. Thus, it is somewhat difficult to dismiss the finding solely on statistical grounds.

PP binds with a high affinity to Y4 receptors found in brain areas involved in the control of food intake (26–28). In fact, Y4 receptor knockout mice are lean, despite elevated circulating concentrations of PP (29). It is very difficult, however, to understand how fasting, but not postprandial PP, may be a marker of this central orexigenic effect. Downregulation of central Y4 receptors is an unlikely explanation because this would blunt the central orexigenic effect of PP and predict no, or an inverse, correlation between fasting PP levels in the circulation and body weight changes. It is also not supported by in vitro experiments (30). Early postprandial PP release is primarily under vagal control (1). Because direct injection of PP into the dorsal motor nucleus inhibits vagal tone to the pancreas (31), another possible explanation is that high fasting PP levels tonically inhibit parasympathetic centers in brainstem, thus decreasing early postprandial PP secretion.

The main limitation of the study is that single time point measurements were obtained for both fasting and postprandial PP. Although we have no information on the within-subject variability of fasting PP levels in this study, we acknowledge that in previous studies we have experienced average coefficients of variation as low as 1.7% (15) and as high as 23% (17). In this study, we have used the PP levels measured 30 min after the administration of a meal as a measure of postprandial PP release. However, postprandial secretion of PP is characterized by a rapid first phase that is followed by a slow decline, depending on the macronutrient composition of meal (1). The results of our more recent study (17) showed that in Pima Indians, PP peaks within 30 min after meal ingestion, suggesting that our single time point is a good proxy for early postprandial PP response. However, PP concentration at 30 min after meal ingestion in the later study showed a strong correlation with both early (0–30 min) and 2-h PP responses (area under the curve, $r = 0.85$ and 0.86, respectively; $P < 0.0001$).

In conclusion, our results provide the first evidence that circulating PP concentrations within the physiological range may contribute to the regulation of energy balance in humans. However, this contribution appears to be more complex than anticipated because of the seemingly opposite effects of fasting and postprandial PP concentrations on the risk of future weight gain.

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