

Peptide YY and Glucagon-like Peptide-1 in Morbidly Obese Patients Before and After Surgically Induced Weight Loss

Thomas Reinehr · Christian L. Roth ·
Gerit-Holger Schernthaner · Hans-Peter Kopp ·
Stefan Kriwanek · Guntram Schernthaner

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Abstract

Background Peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) are cosecreted in the same enteroendocrine L-cells of the gut and reported to inhibit food intake additively. However, findings in human studies regarding these peptides are controversial. The aim of this study was to analyze the relationships between fasting PYY, GLP-1, and weight status in morbidly obese patients before and after surgically induced weight loss.

Methods Fasting GLP-1, PYY, glucose, and insulin concentrations; blood pressure; and body-mass index (BMI) were determined in 30 morbidly obese adults (mean BMI

45.8, mean age 40 years) before bariatric surgery [Roux-en-Y gastric bypass (RYGB): $n=19$; gastric banding (GB): $n=11$] and after weight loss (mean 50% excess weight loss) in the course of mean 2 years.

Results GLP-1 concentrations decreased (mean -20 pg/ml; mean -38% ; $p=0.001$) and PYY concentrations increased (mean $+19$ pg/ml; mean $+19\%$, $p=0.036$) after bariatric surgery. The weight loss and changes of GLP-1 were significantly ($p<0.05$) more pronounced after RYGB as compared to GB, whereas the changes of PYY did not differ significantly between the patients who had undergone RYGB or GB.

Conclusions In morbidly obese adults reducing their weight by bariatric surgery, fasting PYY levels increased and GLP-1 concentrations decreased independently of each other. Therefore, the relationship between PYY and GLP-1 seems more complicated than might be anticipated from animal and in vitro studies.

Keywords GLP-1 · PYY · Obesity · Weight loss · Gastric banding · Roux-en-Y gastric bypass

T. Reinehr and C. L. Roth contributed equally to this work.

T. Reinehr (✉)
Vestische Hospital for Children and Adolescents Datteln,
University of Witten/Herdecke,
Dr. F. Steiner Str. 5, 45711 Datteln, Germany
e-mail: T.Reinehr@kinderklinik-datteln.de

C. L. Roth
Pediatric Endocrinology, Children's Hospital and Regional
Medical Center, Seattle, WA, USA

G.-H. Schernthaner
Department of Medicine II, Division of Angiology,
Medical University of Vienna,
Vienna, Austria

H.-P. Kopp · G. Schernthaner
Department of Medicine I, Rudolfstiftung Hospital Vienna,
Vienna, Austria

S. Kriwanek
Department of Surgery, Rudolfstiftung Hospital Vienna,
Vienna, Austria

Introduction

Peptide satiety signals generated by the gastrointestinal tract include pancreatic polypeptide, glucagon-like peptide 1 (GLP-1), oxyntomodulin, cholecystokinin, and peptide YY (PYY) [1]. Interestingly, two of these hormones, PYY and GLP-1, are synthesized and secreted from the same enteroendocrine L cells of the gut [1, 2]. In immunohistochemical analyses of rodent and human colonic mucosa, about 33 to 85% of L cells showed colocalization of PYY and GLP-1, with the remaining granules containing either

GLP-1 or PYY alone [2, 3]. Furthermore, PYY and GLP-1 increased in a correlating manner postprandially in rats and humans [2, 4]. Moreover, PYY and GLP-1 reduce appetite additively in rodents and humans via an enhanced activation of hypothalamic arcuatus neurons [5].

PYY is metabolized by the enzyme dipeptidyl peptidase-IV (DPP-IV), which hydrolyzes PYY_{1–36} to the more bioactive PYY_{3–36} [1]. The half-life of PYY is only a few minutes [6]. PYY slows gastric emptying and gastrointestinal (GI) motility, inhibits secretion of gastric acid and pancreatic exocrine enzymes, and is thought to be involved in the regulation of food intake [1, 7]. Furthermore, PYY increases mean arterial pressure by evoking the posterior hypothalamic nucleus (PHN) in rodents and regulates autonomic sympathetic outflow to regulate energy expenditure [8, 9]. Recent findings suggest that low plasma PYY levels may contribute to diet-induced human obesity because fasting PYY concentrations correlated negatively with body-mass index (BMI) [10, 11] and injection of PYY decreased caloric intake in humans [10]. These observations were hailed as a potential advance towards an effective antiobesity treatment with PYY. However, the pharmacological value of PYY remains controversial [12, 13].

GLP-1 is synthesized and secreted in two major molecular forms with equipotent biological activity (GLP-1_{7–36} amide and GLP-1_{7–37}) [14]. Endogenous concentration is low in the fasting state and increases in response to a meal [14]. Secreted GLP-1 has only a short half-life over a few minutes and is rapidly inactivated by the DPP-IV [15, 16]. GLP-1 is believed to be the most potent insulinotropic hormone known to date [14, 17]. GLP-1 stimulates insulin secretion in a glucose-dependent manner postprandially and stimulates β -cell proliferation and differentiation in vivo in rodents [14, 17]. Similarly to PYY, GLP-1 inhibits gastric emptying and GI motility and inhibits gastric acid and pancreatic secretion [14, 18]. In addition, infusions of GLP-1 increase satiety and decrease food intake [14, 17].

Nevertheless, the roles of PYY and GLP-1 in obesity remain poorly understood. It is unknown whether the alterations of these hormones are a consequence of being overweight or, conversely, a cause of being overweight, as both hormones affect food intake. To understand the relationship between PYY and GLP-1 and their role in obesity, it would be helpful to study morbidly obese subjects who have lost weight. Because PYY and GLP-1 are cosecreted in the gut, the type of bariatric surgery may influence the concentrations of these hormones and could explain, at least in part, the effect of weight loss. Studies concerning PYY and GLP-1 are limited in morbidly obese patients with surgically induced weight loss. Therefore, the aim of this study was to analyze the relationships between fasting PYY, GLP-1, and weight status in morbidly obese

subjects before and after surgically induced weight loss based on Roux-en-Y gastric bypass or gastric banding.

Methods

Subjects

The study was comprised of 30 morbidly obese adults (mean age 40 ± 12 years; 26 females, 4 males; mean BMI 45.7 ± 7.4 kg/m²) prior to bariatric surgery and at mean 2 years after surgically induced weight loss. Surgery was indicated according to the guidelines of the National Institutes of Health consensus statement for surgery in severe obesity [19]. Patients were systematically referred to a multidisciplinary team for medical, psychological, nutritional, and surgical expertise. Surgery was indicated for patients with a history of repeated failures with conservative nonsurgical techniques. The patients underwent laparoscopic Roux-en-Y gastric bypass (RYGB) ($n=19$) or gastric banding (GB) ($n=11$). Band adjustments were performed as necessary in follow-up. All patients attended the postoperative care follow-up program organized by the multidisciplinary team. Excess weight (EW) was calculated by weight–normal weight using the formula of Broca to define normal weight ($=\text{height in cm}-100$). Mean excess weight loss (EWL) was calculated by weight loss in kilograms divided by normal weight $\times 100$.

Ethical Aspects

The study was approved by the institutional ethics committee and complies with the Declaration of Helsinki, including current revisions, and the Good Clinical Practice guidelines. The procedures followed were in accordance with institutional guidelines. All subjects were carefully instructed about the aims of the study, and written, informed consent was obtained.

Blood Sampling and Determinations

Blood sampling was performed in all subjects in the fasting state at 08:00 A.M. Serum specimens for PYY and GLP-1 were frozen at -81° , whereas all other laboratory determinations were performed directly. All analyses were performed twice and averaged. The assay for PYY was run in one batch with the same standard and the same incubation times from aliquots that had been thawed only once. Total PYY concentration was measured by high-specific radioimmunoassay (RIA) [human PYY (total) RIA Kit, Linco Research, St. Charles, MO, USA] that detects both the cleaved form (PYY_{3–36}) and full-length hormone (PYY_{1–36}) without cross-reactions to NPY, GLP-1, and insulin. The

intra- and interassay coefficients of variation (CV%) were 8%. The minimal detectable concentration was 10 pg/ml. GLP-1 concentrations were measured by a high-specific enzyme-linked immunosorbent assay (human active GLP-1 ELISA Kit™, Linco Research) for GLP-1(7–36 amide) and GLP-1(7–37) without cross-reactions to glucagon or to other forms of GLP-1. All values of GLP-1 were comprised of GLP-1(7–36 amide) and GLP-1(7–37). The sensitivity stated by the manufacturer was 6.6 pg/ml, whereas we determined a sensitivity of 1.7 pg/ml. The intra- and interassay CV% were 12 and 10%, respectively. The assay for GLP-1 was run in one batch with the same standard and the same incubation times from aliquots that had been thawed only once. For quantification of insulin concentrations, an ELISA system was used (Enzymuntest Insulin, ES 600, Boehringer, Mannheim, Germany), for which the intra- and interassay CV% were 3.5 and 5.6%, respectively. Blood glucose concentrations were measured by enzymatic in vitro tests (Roche, Basel, Switzerland); the intra- and interassay CVs were 1.1 and 2.9%. Blood pressure was measured with a mercury sphygmomanometer under resting conditions.

Statistics

Statistical analysis was performed using the Winstat™ software package. Apart from GLP-1, all variables were normally distributed. Therefore, GLP-1 was log transformed. Differences were tested with paired *t* test or Wilcoxon test as appropriate. Bonferroni adjustment was used for multiple tests. Partial correlations adjusted for changes of EW were used to analyze the relationship between changes of blood pressure and insulin and the changes of PYY and GLP-1. Changes were calculated as variable at follow-up–variable prior to bariatric surgery. A *p* value <0.05 was considered as significant. Data are presented as mean values and standard deviation.

Results

Age, gender, and degree of overweight of the 30 patients prior to bariatric surgery and after surgically induced weight loss are shown in Table 1 separated to type of bariatric surgery. The patients did not differ in respect of age (*p*=0.171) or gender (*p*=0.609) at baseline. Mean excess weight loss (EWL) was 50±9% (mean weight reduction 34±18 kg, mean BMI reduction 12±7 kg/m²) in mean 2 years after bariatric surgery. Decrease of weight loss was significantly (*p*=0.044) greater in patients who had undergone RYGB (mean 60±7% EWL, mean weight loss 39.4±4.4 kg) as compared to patients with GB (mean 38±11% EWL, mean weight loss 26.1±7.3 kg).

Table 1 Weight status (weight, BMI), blood pressure, glucose, and insulin concentrations in 30 morbidly obese patients before bariatric surgery and at follow-up after in mean 2 years

	RYGB	GB
Number	19	11
Age (years)	39±12	41±12
Gender	84% female	91% female
Weight (kg)		
Baseline	130±24	126±14
At follow-up	90±16*	97±24*
BMI (kg/m ²)		
Baseline	46.7±8.8	45.2±4.8
At follow-up	32.1±5.7*	34.6±9.7*
Systolic BP (mmHg)		
Baseline	142±13	142±12
At follow-up	121±15*	123±26*
Diastolic BP (mmHg)		
Baseline	87±8	88±6
At follow-up	79±9*	81±11
Fasting glucose (mg/dl)		
Baseline	87±9	90±11
At follow-up	78±20*	84±8*
Fasting insulin (mU/l)		
Baseline	24±16	22±9
At follow-up	7±4*	9±5*

Data as mean ± standard deviation.

BP = blood pressure.

**p*<0.05 baseline vs follow up.

PYY increased (102±7 pg/ml → 122±10 pg/ml; *p*=0.036), whereas GLP-1 decreased (52±14 pg/ml → 32±14 pg/ml; *p*=0.001) after both types of bariatric surgery (see Fig. 1). The increase of PYY did not differ significantly (*p*=0.704) between the patients who had undergone RYGB or GB. However, the decrease of GLP-1 was significantly (*p*=0.008) higher in the patients who had undergone RYGB as compared to the patients who had undergone GB. The PYY concentrations and the GLP-1 concentrations did not differ significantly at baseline between the subjects who had undergone RYGB or GB.

The changes of PYY were not significantly related to changes of GLP-1 in partial correlations adjusted for changes of EW (*r*=0.24). Changes of EW were not significantly related to changes of PYY (*r*=−0.24) nor changes of GLP-1 (*r*=0.11). In partial regression adjusted for changes of EW, changes of GLP-1 were significantly positively related to changes of fasting insulin (*r*=0.52, *p*=0.003). Changes of fasting glucose (*r*=−0.01), systolic (*r*=0.18), and diastolic (*r*=0.16) blood pressure did not correlate significantly to changes of GLP-1 in partial regression adjusted for changes of EW. In partial regression adjusted for changes of EW, changes of PYY were significantly positively related to changes of blood pressure (Fig. 2). Changes of fasting insulin (*r*=0.25) and glucose

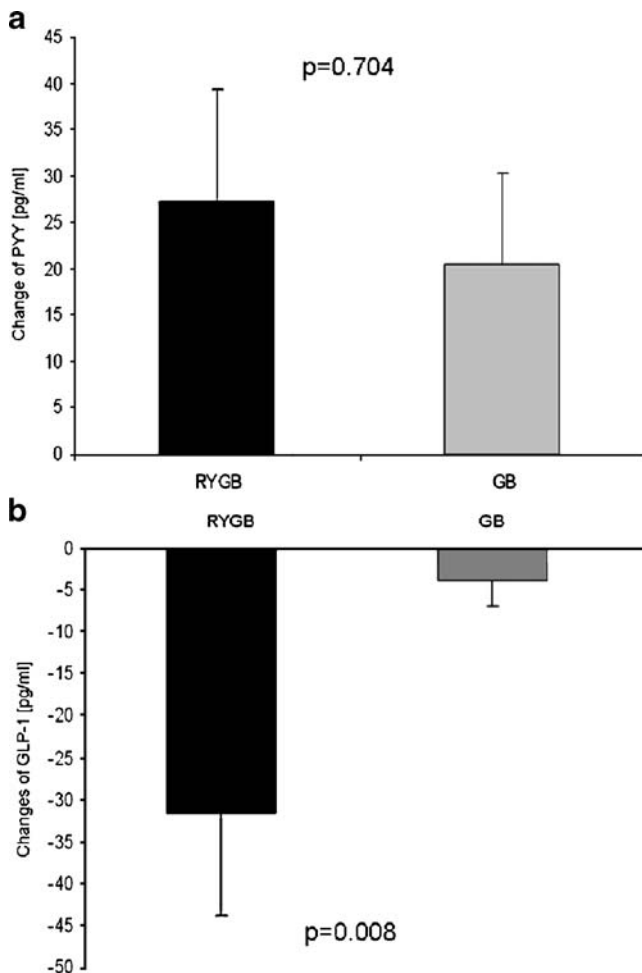


Fig. 1 Fasting PYY (a) and GLP-1 (b) concentrations before and after Roux-en-Y gastric bypass (RYGB) ($n=19$) and gastric banding (GB) ($n=11$) in morbidly obese adults (data as mean and standard deviation; change of variable=variable after weight loss–variable before bariatric surgery; p : derived from comparison between RYGB and GB)

($r=0.14$) did not correlate significantly to changes of PYY in partial regression adjusted for changes of EW.

Discussion

Surprisingly, fasting GLP-1 and PYY concentrations did not change in a correlating manner as GLP-1 significantly decreased and PYY significantly increased in our long-term postsurgery follow-up study of obese adults who had undergone weight-reduction surgery. These findings seem to be out of sync with the theory of simultaneous release of both PYY and GLP-1 from L cells. According to this theory, Naslund et al. reported a correlating increase of fasting PYY and GLP-1 after jejunoileal bypass [20]. However, their study was based on a very small sample size ($n=7$) and a different surgical approach with exclusion

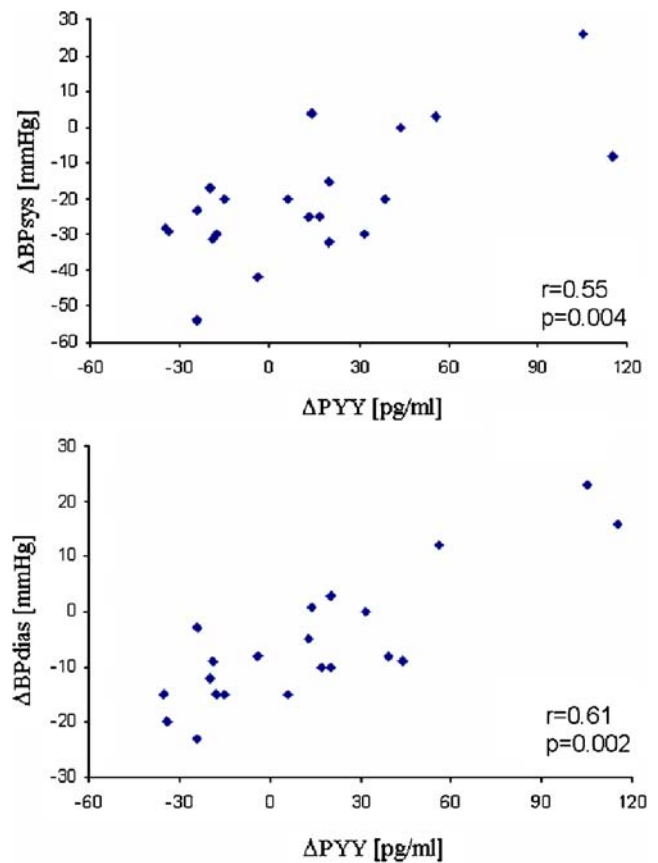


Fig. 2 Changes of blood pressure in relation to changes of PYY in 30 morbidly obese adults with surgically induced weight loss (partial regression analysis adjusted for changes of EW; BP , blood pressure; Δ variable=variable after weight loss–variable before bariatric surgery)

of parts of the jejunum, and the follow-up period was much longer (20 years). These factors may explain the difference from our study.

Our findings suggest that GLP-1 and PYY are regulated differently in obese subjects. A clue to this incongruence could be reports that have found that the secretion of GLP-1, but not of PYY, is modulated by leptin concentrations that are found to significantly correlate with decreases in weight loss [4, 21, 22]. Although the leptin receptor is predominantly distributed in the ventral medial hypothalamic region known to be important in determining feeding behavior [23], it is now recognized that the leptin receptor is also expressed in several peripheral tissues, including the gut and the pancreas [24, 25]. Physiological concentrations of leptin were demonstrated to stimulate GLP-1 secretion from rat, mouse, and human L cells in a dose-dependent fashion [22].

Possible Implications of the Decrease of GLP-1 Levels

In our study, fasting GLP-1 decreased after surgically induced weight loss, a result that is in concordance with

weight loss studies based on hypocaloric diet [26, 27]. This would bolster the hypothesis that weight loss rather than surgery seems to be the major determinant of decreasing fasting GLP-1 concentrations because a separate study found that, 6 weeks after RYGB, fasting and postprandial GLP-1 concentrations remained unchanged [28]. However, RYGB was associated with a greater decrease of fasting GLP-1 as compared to GB in our study, suggesting also a surgical effect of the exclusion of the duodenum on the concentrations of the gut hormone GLP-1. Because the changes of GLP-1 were not correlated to changes of weight status in our study, the greater weight loss in RYGB does not seem to explain exclusively the greater decrease of fasting GLP-1 levels in RYGB as compared to GB.

In contrast to the finding in the fasting state, a postprandial increased secretion of GLP-1 has been reported after weight loss [29], which was hypothesized to normalize the glucose metabolism in diabetic patients. However, the postprandial secreted GLP-1 is inactivated immediately [16]. Moreover, Morinigo et al. demonstrated in a prospective study that the incremental area under the curve of GLP-1 in response to a standard test meal increased in obese patients with normal or impaired glucose tolerance but not in subjects with diabetes at 6 weeks after undergoing RYGB, but fasting plasma glucose and HbA1c decreased in patients with normal and impaired glucose tolerance, as well as patients with diabetes [30]. This would indicate that GLP-1 does not seem to be a critical factor for changes in glucose metabolism.

In our study, the changes of fasting GLP-1 were significantly correlated to changes of fasting insulin even after adjustment to changes of weight status. Therefore, there could be a relationship between GLP-1 and insulin concentrations in the fasting state. The mechanism of this relationship seems to be different from the postprandial state. GLP-1 has been reported to stimulate insulin secretion postprandially in a glucose-dependent manner [16], yet changes of fasting GLP-1 were not related to changes of glucose in our study. Clearly, further studies are necessary to analyze the relationship between fasting insulin and GLP-1 and to prove an actual causal relationship.

Possible Implications of the Increase of PYY Levels

In our study, RYGB- and GB-induced weight loss was associated with a remarkable increase of fasting PYY in concordance with previous studies with extensive weight loss based on diet [11], vertical banded gastroplasty [31], and jejunoileal bypass [20]. Yet, in two small studies, no increase of fasting PYY was observed after RYGB ($n=9$, mean baseline BMI 34.2 kg/m², mean 36% EWL), after GB ($n=9$, mean baseline BMI 35.8 kg/m², 25% EWL) [32], or after hypocaloric diet ($n=17$, mean baseline BMI

35.1 kg/m², 5% EWL) [12]. The smaller sample sizes, the lower degree of overweight at baseline, and the smaller degree of weight loss in the diet study might explain these contrasting findings. Because PYY increased after weight loss in most studies, the decrease of PYY in obese patients could indicate a consequence of being overweight and not a cause of overweight.

Although PYY is secreted in the gut, neither type of bariatric surgery (GB or RYGB) significantly influenced the postsurgical measurements of fasting PYY concentrations in our study. However, a trend of greater increase of PYY post-RYGB surgery compared to post-GB surgery occurred in our study in concordance with a postprandial study [29]. Because our study sample was moderate, the lack of significance may be caused by a lack of power. Because PYY decreases appetite by central and peripheral actions [1, 7, 10], we suspect that this change of gut hormone profile helps to both achieve and maintain weight loss after bariatric surgery.

Interestingly, increasing PYY levels after weight loss were related to a lower decrease of blood pressure values even after adjustment to changes of weight status. This finding may suggest an increasing blood pressure effect of fasting PYY. Accordingly, injection of PYY in the posterior hypothalamic nucleus of rats increased mean arterial pressure [8, 9]. Further studies are necessary to prove the impact of PYY on blood pressure.

Methodical Considerations

This study has some potential limitations. First, BMI was used to classify overweight. Although BMI is a good measure for overweight, one needs to be aware of its limitations as an indirect measure of fat mass. Second, changes of dieting may have also influenced our findings, as GLP-1 and PYY concentrations are reported to be influenced by dietary factors [17, 33]. Third, this study does not discriminate between the isoforms of PYY and GLP-1. Fourth, we measured PYY and GLP-1 levels only in the fasting state and not postprandially during weight loss. Because impaired PYY and GLP-1 release in response to a meal has been reported in obese subjects [34], postprandial measurement of both of these hormones should be studied in subjects on an extensive weight-loss program. Finally, DPP-IV inhibitor was not added, potentially leading to too-low concentrations of the analyzed GI hormones, although our samples were immediately centrifugated and frozen. However, we compared baseline with follow-up data, which were both performed without DPP-IV inhibitors. Therefore, a systematic error seems highly unlikely.

In summary, fasting PYY levels increased and fasting GLP-1 concentrations decreased independently of each other in morbidly obese adults with surgically induced

weight reduction. Therefore, although they are both synthesized by and secreted from the same enteroendocrine L cells of the gut, the relationship between these gut hormones seems to be more complicated than might be indicated by previous *in vitro* and animal studies. Further prospective research is required to examine the relationship between GLP-1, PYY, and weight status in humans, especially in light of the ever-increasing importance of identifying the discrete mechanisms of the neuroendocrine regulation of human energy homeostasis.

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