gastrointestinal disorders

MDPI

Article

Peptide YY and Glucagon-like Peptide-1 Secretion in Obesity

Jennifer Wilbrink [1,2,3], Mark van Avesaat [1], Arnold Stronkhorst [2], Freddy Troost [1,4], Carel W le Roux [5] and Ad Masclee [1,*]

[1] Division of Gastroenterology-Hepatology, Maastricht University Medical Center, NUTRIM—School for Nutrition and Translational Research in Metabolism, 6229 Maastricht, The Netherlands; j.wilbrink@zuyderland.nl (J.W.); m.vanavesaat@zuyderland.nl (M.v.A.); f.troost@maastrichtuniversity.nl (F.T.)
[2] Department of Gastroenterology-Hepatology, Catharina Hospital, 5623 Eindhoven, The Netherlands; a.stronkhorst@hetnet.nl
[3] Department of Gastroenterology-Hepatology, Zuyderland Medical Centre Sittard-Geleen, 6162 BG Geleen, The Netherlands
[4] Food Innovation and Health, Centre for Healthy Eating and Food Innovation, NUTRIM—School for Nutrition and Translational Research in Metabolism, Maastricht University, 6220 MD Venlo, The Netherlands
[5] Diabetes Complications Research Centre, Conway Institute, University College Dublin, D04 V1W8 Dublin, Ireland; carel.leroux@ucd.ie
* Correspondence: a.masclee@mumc.nl

Abstract: Objective: The regulation of food intake is disturbed in obesity, possibly resulting from alterations in gut peptide secretion. We hypothesize that obesity is associated with attenuated systemic and tissue concentrations of the gut peptides PYY and GLP-1. **Methods**: A prospective single-center study in which we included 13 individuals with obesity (BMI 39.5 ± 2.8 kg/m^2) and 11 lean individuals as controls (BMI 20.7 ± 1.2 kg/m^2) matched for age and gender. We measured: (1) tissue concentrations and mRNA expression of GLP-1 and PYY in ileal and colonic biopsies taken during routine colonoscopy and (2) plasma concentrations of PYY and GLP-1 in response to a meal in the same group. **Results**: Plasma GLP-1 and PYY responses did not differ between individuals with obesity and lean controls. Neither were tissue concentrations and mRNA expression of both peptides different between both groups. **Conclusions**: Systemic and local PYY and GLP-1 concentrations in individuals with obesity do not differ from those in lean subjects.

Keywords: PYY; GLP-1; secretion; morbid obesity

Academic Editor: Takuji Tanaka

Received: 25 November 2024
Revised: 20 December 2024
Accepted: 26 December 2024
Published: 30 December 2024

Citation: Wilbrink, J.; van Avesaat, M.; Stronkhorst, A.; Troost, F.; le Roux, C.W.; Masclee, A. Peptide YY and Glucagon-like Peptide-1 Secretion in Obesity. *Gastrointest. Disord.* **2025**, *7*, 3. https://doi.org/10.3390/gidisord7010003

1. Introduction

In people with obesity, the regulation of food intake is disturbed. This has been associated with alterations in regulatory mechanisms, including secretion of proximal and distal gut peptides, such as ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY) [1,2].

For individuals with morbid obesity resistant to conventional therapy, bariatric surgery is currently the most effective treatment to achieve long-term weight loss. After Roux-en-Y gastric bypass (RYGB), significant weight loss has been observed with marked improvement in glucose tolerance [3]. These beneficial effects result from a combined restrictive and malabsorptive procedure leading to accelerated emptying from the gastric pouch to a more distal part of the small intestine. Consequently, the distal small intestine is exposed to larger quantities of ingested nutrients, leading to enhanced distal gut hormone responses such as of GLP-1 and PYY. Nowadays, the use of GLP-1 analogues for the treatment of diabetes and obesity is rapidly expanding based on significantly better glycemic control, increased satiation, and significant weight loss compared to lifestyle modifications alone [4,5].

Determining whether postprandial gut peptide secretion is affected in individuals with obesity compared to lean individuals may help us to better understand the pathophysiology of obesity. Aukan et al. [6], in a systematic review and meta-analyses, have recently pointed to attenuated postprandial responses of total ghrelin and total PYY in people with obesity. Postprandial GLP-1 responses were not significantly different between obese and lean individuals, but a trend was noted towards attenuated GLP-1 responses to a high-caloric meal in obese versus lean individuals.

It is not known whether these attenuated postprandial responses result from impaired gut peptide secretion or from reduced sensitivity of gut endocrine cells to nutrient stimuli. In order to answer this question, we studied, in healthy lean controls and individuals with obesity, (a) fasting GLP-1 and PYY plasma levels and postprandial responses of GLP-1 and PYY and (b) GLP-1 and PYY tissue concentrations and mRNA expression of GLP-1 and PYY in distal ileum and proximal colon biopsies of these subjects.

2. Materials and Methods

This study was performed according to the principles of the Declaration of Helsinki (amended in 2013, Fortaleza, Brasil). The Research and Ethical committees of the Catharina Hospital in Eindhoven had approved the study protocol. Participants gave written informed consent prior to participation. Subjects who were about to undergo a colonoscopy for surveillance of colonic polyps were recruited from the department of Gastroenterology–Hepatology. A total of 13 individuals with obesity (BMI 39.5 $\pm$ 2.8 kg/m^2) and 11 lean controls (BMI 20.7 $\pm$ 1.2 kg/m^2) matched for age and gender with a stable weight for the last three months were included in th study. Exclusion criteria were chronic illness or previous gastrointestinal surgery influencing eating behavior, gastrointestinal absorption or transit, pregnancy, metabolic disorders, psychiatric illness, eating disorders, substance abuse, and extreme exercising. The use of psychotropic drugs was not allowed. Medication potentially influencing motility was discontinued.

2.1. Experimental Design

2.1.1. Tissue Sampling

In all subjects, bowel preparation was identical and consisted of a macrogol solution. (Klean Prep or Movi Prep, Norgine Amsterdam, The Netherlands). During colonoscopy, 8 biopsies were taken from previously defined areas: 4 biopsies from the ascending colon (5–10 cm distal to the ileocecal valve) and 4 biopsies from the distal 10 cm of the terminal ileum, using standard biopsy forceps. After sampling, the tissue samples were snap-frozen in liquid nitrogen and stored at -80 °C until analysis.

2.1.2. Plasma GLP-1 and PYY

After the colonoscopy procedure had been performed, subjects were planned for a meal test on a separate day, with an interval of at least 14 days. For the meal stimulation test, subjects arrived after a 12 h overnight fast at our research facility at 8:30 AM. An intravenous cannula was inserted to facilitate drawing of blood samples. At 9:00, subjects ingested 300 g of a commercially available high-fat yoghurt (Almhof Müller, Veenendaal, The Netherlands), containing 8 g fat/100 g, 15.2 g carbohydrates/100 g, and 2.9 g proteins/100 g (total 435 Kcal). Blood samples were drawn at regular intervals: before and at 30, 60, 90, and 120 min after meal ingestion. Samples were centrifuged and the supernatant plasma was stored at -20 °C until determination.

2.1.3. Measurement of Plasma Active GLP-1 and PYY

Blood was collected in ice-chilled tubes (Vacutainer, Beckton Dickinson, Plymouth, UK) containing EDTA and 10 µL DDPIV inhibitor per ml of blood (DDPIV-inhibitor, Nuclilab BV, Ede, The Netherlands) to prevent immediate degradation, e.g., conversion of GLP-1 and PYY by dipeptidyl peptidases IV. After the last sample was taken, the tubes were centrifuged (3000 rpm, 15 min at 4 °C). The supernatant plasma was stored at –20 °C until determination. Active GLP-1 (included both 7–36 and 9–36) was determined with the use of a GLP-1 ELISA kit (EZGLP1T-36K; Millipore, Linco Research, St. Louis, MO, USA) with a range of 4–1000 pmol/L and an intra-assay CV of <5% (EZGLP1T-36K; Millipore, Linco Research, St. Louis, MO, USA). Total PYY (included both peptide YY1–36 and peptide YY3–36) was measured with the use of a Human PYY (Total) ELISA kit (EZHPYYT66K; Millipore) with an intra-assay CV of 3% (EZHPYYT66K; Millipore, Linco Research).

2.1.4. Measurement of Tissue GLP-1 and PYY

Snap-frozen tissue samples obtained during colonoscopy were defrozen. Samples were placed into preheated polypropylene tubes containing 0.5% acetic acid. The weight of wet tissue samples was measured and the acetic acid was adjusted accordingly (10 mL/g). The samples were held at 100 °C in a vigorously boiling water bath for 15 min. After a further 30 min at room temperature, the supernatant was used to measure PYY and GLP-1 immunoreactivity as previously described [1].

2.1.5. Measurement of GLP1- and PYY mRNA in Tissue

Measurement of GLP1- and PYY mRNA in tissue was performed by quantitative PCR analysis with RNA isolation. Total RNA was isolated using a TRIzol lysis assay. Next, total RNA was hybridized onto GeneChip microarrays (HG U133A; Affymetrix Inc., Santa Clara, CA, USA) according to the manufacturer's instructions. Briefly, 1 mL TRIzol (Invitrogen Life Technologies b.v., Breda, The Netherlands) and 10 µL ß-mercaptoethanol (VWR International b.v., Amsterdam, The Netherlands) were added to each frozen tissue sample and shaken with a minibeadbeater for 30 s. A total of 200 µL Chloroform (Sigma Aldrich Chemie b.v., Zwijndrecht, The Netherlands) was added and the samples which were incubated for 3 min, followed by phase separation using centrifugation at 21,000× *g* for 15 min. The upper aqueous phase was taken and 500 µL 70% ethanol was added. Subsequently, the extracted RNA was purified using the RNeasy Mini Kit (Qiagen Benelux b.v., Venlo, The Netherlands) with extra DNA digestion by on-column RNase-Free DNase treatment (Qiagen Benelux b.v., Venlo, The Netherlands). *qPCR* First Strand cDNA was synthesized using the iScript cDNA Synthesis kit (Bio-Rad, Veenendaal, The Netherlands) according to the manufacturer's instructions. In total, 500 ng total RNA was used as template for the cDNA reaction. The cDNA was diluted with RNase free H_2O to a concentration of 5 and 10 ng/µL, respectively. IQ Sybr Green Supermix (Bio-Rad, The Netherlands) was used for the Q-PCR. Each Q-PCR reaction of the Q-PCR contained 12.5 µL iQ Sybr Green Supermix, 1 µL of 10 µM gene-specific forward and reverse primers, 2 µL cDNA template solution, and 8.5 µL sterile water. Reactions were run on the My IQ Single Color Real Time PCR Detection System (Bio-Rad, Veenendaal, The Netherlands). The cycling conditions comprised a period of 3 min at 95 °C and 40 cycles at 95 °C for 10 s and 60 °C for 45 s followed by a melting program. The CT values were normalized using the IQ5 Optical System Software version 2.0 (Bio-Rad, Veenendaal, The Netherlands). Data were presented as normalized expression ratios, i.e., expression of target genes normalized to reference gene Glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

2.1.6. Measurements of Satiety

During the meal test, subjective parameters such as satiety, fullness, feelings of hunger, desire to eat, and prospective feeding intentions were scored on a 100 mm visual analogue scale (VAS), as described previously by Blundell and Silverstone [7,8].

2.2. Statistical Analysis

Plasma and tissue PYY and GLP-1 concentrations and incremental postprandial area under the curve (iAUC) secretion between individuals with obesity and lean controls were analyzed using t6test or Mann–Whitney test, when appropriate. A Chi square test was used to analyze demographic characteristics (sex, age, etc.). The VAS-scores were statistically analyzed using the incremental AUC (iAUC) data after the meal test. An unpaired *t*-test was used to analyze the data. A *p*-value of 0.05 was considered statistically significant.

3. Results

3.1. Subjects

A total of 13 individuals with severe obesity and 11 lean age and gender-matched controls (BMI) underwent colonoscopy. The mean age was 51.3 years (±SD12.2) in the group with obesity and 50.4 years (±SD12.3) in the lean group. From this group, a total of 10 individuals with obesity (BMI 39.5 ± 2.8 kg/m^2) and 10 lean individuals (BMI 20.7 ± 1.2 kg/m^2) subsequently underwent the meal test. In each group, seven females and three males participated. Waist circumference differed significantly ($p < 0.05$) in both groups (121.0 ± 7.2 cm in the group with obesity and 78.2 ± 5.3 cm in the lean group).

3.2. Tissue GLP-1 and PYY and mRNA Expression

Tissue concentrations of GLP-1 and PYY and tissue-relative mRNA expression were measured in distal ileum and proximal colonic biopsies. Tissue GLP-1 and PYY concentrations (pmol/L) were not significantly different between individuals with obesity and lean subjects, neither in ileal nor in colonic biopsies (Table 1). Neither were tissue-relative GLP-1 and PYY mRNA expression significantly different in colonic or ileal biopsies of individuals with obesity versus lean controls, after correction for multiple testing (Table 1).

Table 1. Tissue concentrations (pmol/L) and mRNA expression of GLP-1 and PYY in colonic and ileum biopsies of individuals with obesity and lean individuals (median and interquartile ranges). The mRNA data are presented as expression of target genes normalized to reference gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

		Obese Subjects	**Lean Subjects**	**Uncorrected *p* Value**	**Corrected Benjamini Hochberg *p* Value**
Ileum	GLP-1 (tissue)	94.8 [59.9–121.1]	186.3 [108.7–224.4]	0.029	0.116
	PYY (tissue)	328 [203.3–702.0]	403.3 [239.7–729.6]	0.86	0.86
	GLP-1 (mRNA)	0.55 [0.38–0.87]	0.64 [0.39–1.13]	0.75	0.86
	PYY (mRNA)	0.99 [0.48–1.37]	0.75 [0.40–1.26]	0.65	0.86
Colon	GLP-1 (tissue)	9.35 [7.1–12.6]	8.9 [7.2–17.1]	0.96	0.96
	PYY (tissue)	441 [168–639]	269 [176–556]	0.70	0.933
	GLP-1 (mRNA)	0.35 [0.20–0.48]	0.76 [0.33–1.63]	0.043	0.126
	PYY (mRNA)	0.99 [0.71–1.39]	1.98 [0.92–3.72]	0.063	0.126

3.3. Plasma GLP-1 and PYY

Basal plasma active GLP-1 and PYY concentrations were not significantly different between individuals with obesity and lean subjects (Figure 1). Neither were postprandial plasma PYY and GLP-1 levels significantly different between individuals with obesity and lean subjects. The incremental postprandial AUC for PYY and GLP-1 did not differ significantly between individuals with obesity and lean individuals (iAUC GLP-1 $p = 0.25$ and iAUC PYY $p = 0.41$).

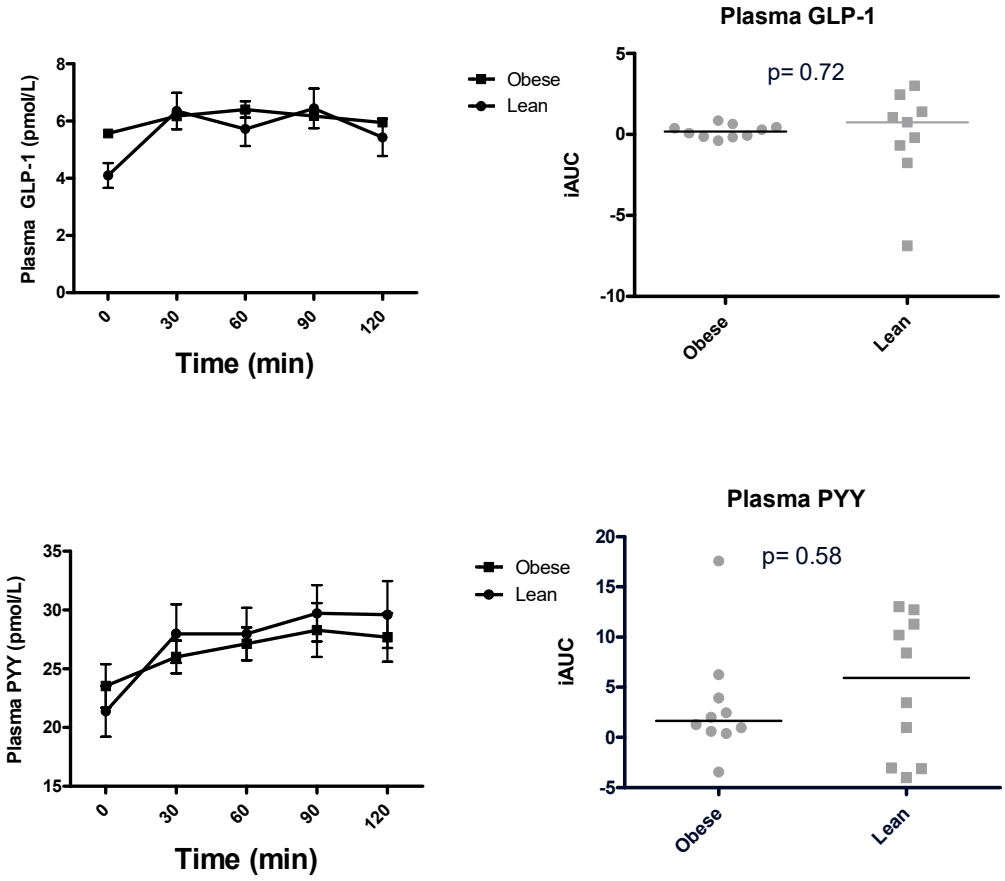

Figure 1. Plasma active GLP-1(pmol/L) and total PYY (pmol/L) concentrations (left panels) and individual incremental postprandial iAUC (pmol/L.120 min; right panels) in lean individuals and individuals with obesity.

3.4. Satiety Scores

From the VAS scores for satiety, only fullness, satiety, and hunger are shown in Figure 2, but data on desire to eat and prospective feeding intentions are not shown. For none of the satiety parameters were significant differences seen between individuals with obesity and lean individuals. After meal ingestion, fullness and satiety increased significantly over basal conditions while hunger, prospective feeding intentions, and desire to eat decreased significantly in both the lean group and the individuals with obesity. The incremental postprandial AUC scores for fullness, satiety, hunger, desire to eat, and prospective feeding intentions were not significantly different between lean individuals and individuals with obesity.

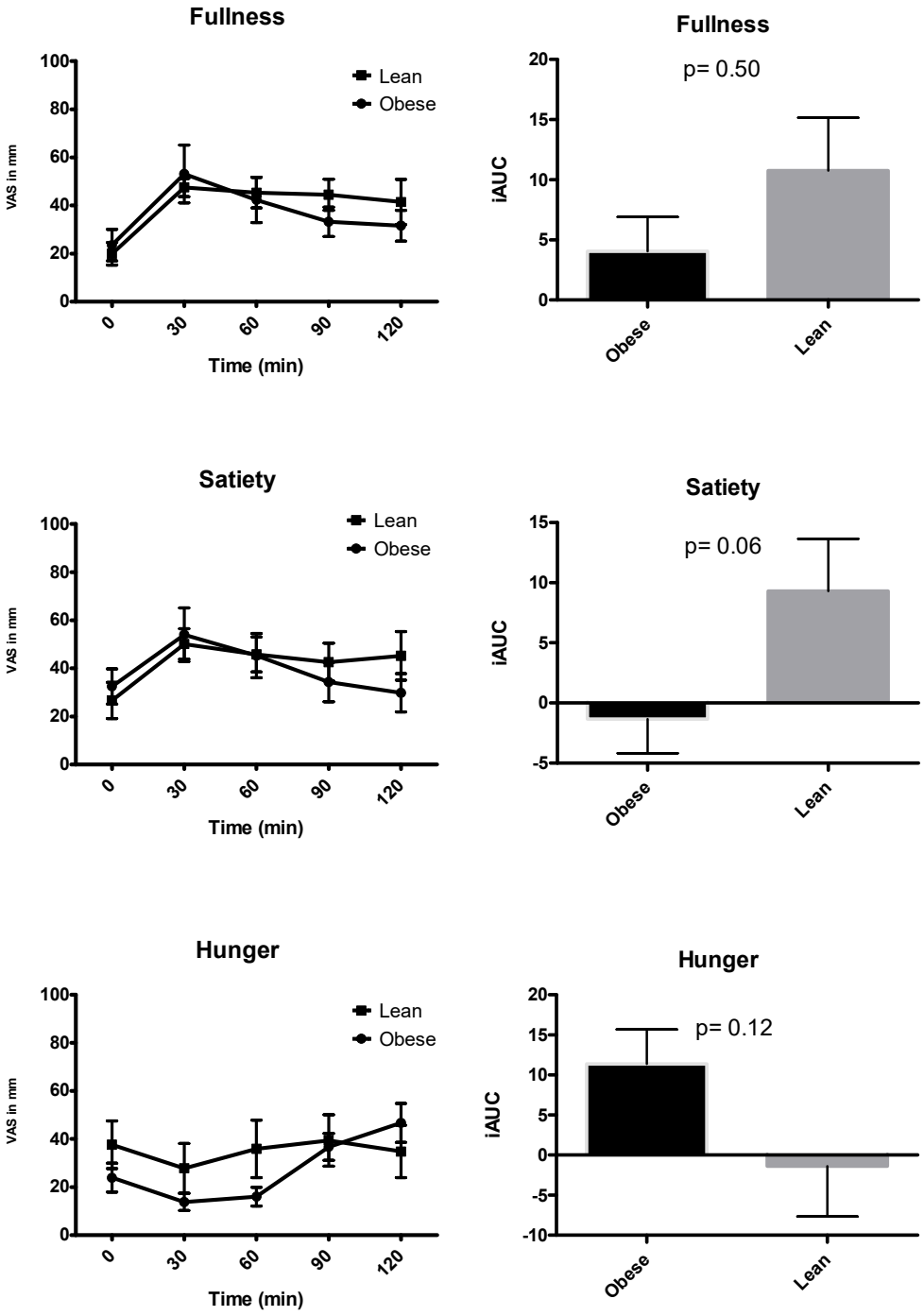

Figure 2. Absolute VAS scores and incremental AUC of satiety parameters in lean individuals and individuals with obesity before and after meal ingestion. The meal was ingested at t = 0 min.

4. Discussion

We evaluated the PYY and GLP-1 concentrations in plasma and tissue and we measured tissue mRNA expression of PYY and GLP-1 in lean individuals and individuals with obesity. No significant differences were found in tissue and plasma concentrations, nor in tissue mRNA expression of PYY and GLP-1 between the two groups. Postprandial responses did not differ between individuals with obesity and lean individuals. Our results are in line with several previously published studies [9–11]. On the other hand, Aukan et al. [6], in a recent systematic review and meta-analysis, pointed to attenuated postprandial responses of ghrelin and PYY in people with obesity. In that review, the postprandial GLP-1 responses were not significantly different between obese and lean individuals. How-

ever, a trend was seen towards attenuated GLP-1 responses to a high-caloric meal (750 kcal) in obese vs. lean individuals. After low caloric meals, the differences in GLP-1 responses between obese and lean individuals were no longer present [6]. Our finding of postprandial gut peptide responses in the same range in obese and lean individuals may result from the lower caloric meal we used (435 kcal).

The large variation in the reported data on postprandial gut peptide secretion in obese versus lean people may result from factors such as caloric and macronutrient composition and texture of the meal, but it may also depends on the severity of obesity [6,11–16]. Aukan et al. investigated peptide responses in individuals with different BMI classes and found more attenuated gut peptide responses in the subclass with the highest BMI [16].

The question arises whether diabetes mellitus and/or impaired glucose intolerance are factors associated with the GLP-1 response. Manell et al. [17] observed impaired GLP-1 responses in patients with obesity and type 2 diabetes. The AUC of GLP-1 in individuals with impaired glucose tolerance was not different from non-diabetic individuals. This finding suggests that an impaired GLP-1 response is associated with longstanding obesity in the presence of insulin resistance and type 2 diabetes. This observation has been confirmed by Færch et al. [18], who investigated a large group of individuals with obesity with normal and with impaired glucose tolerance and type 2 diabetes. A higher GLP-1 response after OGTT was associated with better insulin sensitivity and B-cell function, older age, and lesser degree of obesity. It should be noted that, in our group, individuals were non-diabetic and did not use any glucose-lowering oral drugs. This may be an additional explanation for our observation that no differences in plasma GLP-1 responses were seen between individuals with obesity and lean controls.

With respect to PYY, Le Roux et al. [1] and Aukan et al. [6] reported on attenuated postprandial responses of PYY in individuals with obesity. Le Roux et al. [1] suggested that obese subjects may have PYY deficiency resulting in reduced satiety, thus reinforcing their obesity. This was confirmed by Witjaksono et al. in another study design after giving equicaloric meals with increasing protein content resulting in similar systemic gut peptide concentrations, also for PYY [19]. In contrast, in our study, we did not observe any differences in PYY levels between individuals with obesity and lean control subjects, neither in plasma nor in tissue levels, nor in tissue mRNA expression.

In our study, the same assay to determine PYY was used as that in the study of Le Roux et al. [1]. Fat is a well-known and powerful stimulus for PYY secretion. The high-fat breakfast meal (24 g fat) that was offered in our study was a strong stimulus that may have overridden the subtle differences in PYY secretion between individuals with obesity and lean controls found by Le Roux et al. [1].

Jorsal et al. [20] have investigated mRNA expression of GCG (GLP-1) and PYY along the intestinal tract in patients with type 2 diabetes and in healthy individuals. The mean BMI was 27 kg/m^2 in both groups. The GLP-1 and PYY expression in the colon was found to be higher in patients with type 2 diabetes. The individuals with obesity we investigated were all non-diabetic. This may explain the fact that we did not find differences in mRNA expression nor in peptide response between individuals with obesity and lean subjects.

We expected to find differences in VAS scores of satiety between individuals with obesity and lean individuals. Studies investigating postprandial satiety/satiation responses in obesity have shown lower VAS scores of satiety/satiation compared to lean individuals. In another study by Debenedictis et al. [12], the investigators found no significant differences in VAS scores between the obese and lean individuals. However, a bias (e.g., giving socially desirable answers) cannot be ruled out.

A strength of our study is that both postprandial gut peptide responses and tissue concentrations/mRNA expressions were measured in the same group of individuals. A

potential weakness of our study may be that we were not able to perform a reliable power calculation. On the other hand, the sample size of our study is of the same magnitude of those in other publications covering the same topic.

Our hypothesis of attenuated GLP-1 and PYY responses in individuals with obesity was not confirmed. Neither plasma levels nor tissue or mRNA concentrations of GLP-1 and PYY were significantly different between lean individuals and individuals with obesity. We found no evidence for an attenuated postprandial response of PYY and GLP-1 in individuals with obesity nor any indication for altered peptide release or mRNA expression.

Incretins such as GLP-1 and GIP and the distal gut peptide PYY are important mediators and regulators of various physiological processes such as satiety and eating behavior. They are also relevant as a link towards strategies to treat and prevent obesity. The availability of effective bariatric procedures and recently also the availability of GLP-1 and GIP analogues in the treatment of obesity are two important and effective steps towards a better management of the obesity pandemic. Further research is needed to better understand the role (of disturbed secretion) of incretins and distal gut peptides in the pathophysiology of obesity.

5. Conclusions

Our data indicate that, at the plasma and tissue level, including mRNA expression, the PYY and GLP-1 responses in individuals with obesity do not differ from lean control subjects.

Author Contributions: Conceptualization, J.W., A.M., A.S. and F.T.; methodology, J.W. and A.M.; software, J.W. and M.v.A.; validation, J.W.; formal analysis, J.W., M.v.A. and C.W.l.R.; investigation, J.W.; resources, J.W.; data curation, J.W. and M.v.A.; writing—original draft preparation, J.W. and A.M.; writing—review and editing, J.W. and A.M.; visualization, J.W. and M.v.A.; supervision, A.M. and A.S.; project administration, J.W.; funding acquisition, J.W. and A.S. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by the Scientific Funding Organization (Wetenschappelijk fonds) of the Catharina Hospital Eindhoven and Gastrostart (a funding for innovative research in gastroenterology granted by the Dutch Gastroenterology Association).

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical ethical committee of Catharina hospital in Eindhoven, METC number M08-1855, CCMO number NL 23155.060.08.

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Acknowledgments: We thank Anton van der Stokker, laboratory analyst, for his support in analyzing and storing blood samples.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. le Roux, C.W.; Batterham, R.L.; Aylwin, S.J.; Patterson, M.; Borg, C.M.; Wynne, K.J.; Kent, A.; Vincent, R.P.; Gardiner, J.; Ghatei, M.A.; et al. Attenuated peptide YY release in obese subjects is associated with reduced satiety. *Endocrinology* **2006**, *147*, 3–8. [CrossRef] [PubMed]
2. Cummings, D.E.; Overduin, J. Gastrointestinal regulation of food intake. *J. Clin. Investig.* **2007**, *117*, 13–23. [CrossRef] [PubMed]

3. Morinigo, R.; Vidal, J.; Lacy, A.M.; Delgado, S.; Casamitjana, R.; Gomis, R. Circulating peptide YY, weight loss, and glucose homeostasis after gastric bypass surgery in morbidly obese subjects. *Ann. Surg.* **2008**, *247*, 270–275. [CrossRef] [PubMed]
4. Wilding, J.P.H.; Batterham, R.L.; Calanna, S.; Davies, M.; Van Gaal, L.F.; Lingvay, I.; McGowan, B.M.; Rosenstock, J.; Tran, M.T.D.; Wadden, T.A.; et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N. Engl. J. Med.* **2021**, *384*, 989–1002. [CrossRef] [PubMed]
5. Rubino, D.M.; Greenway, F.L.; Khalid, U.; O'Neil, P.M.; Rosenstock, J.; Sorrig, R.; Wadden, T.A.; Wizert, A.; Garvey, W.T.; Investigators, S. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults with Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *JAMA* **2022**, *327*, 138–150. [CrossRef]
6. Aukan, M.I.; Coutinho, S.; Pedersen, S.A.; Simpson, M.R.; Martins, C. Differences in gastrointestinal hormones and appetite ratings between individuals with and without obesity-A systematic review and meta-analysis. *Obes. Rev.* **2023**, *24*, e13531. [CrossRef] [PubMed]
7. Blundell, J.; de Graaf, C.; Hulshof, T.; Jebb, S.; Livingstone, B.; Lluch, A.; Mela, D.; Salah, S.; Schuring, E.; van der Knaap, H.; et al. Appetite control: Methodological aspects of the evaluation of foods. *Obes. Rev.* **2010**, *11*, 251–270. [CrossRef] [PubMed]
8. Silverstone, J.T.; Stunkard, A.J. The anorectic effect of dexamphetamine sulphate. *Br. J. Pharmacol. Chemother.* **1968**, *33*, 513–522. [CrossRef]
9. Trahair, L.G.; Marathe, C.S.; Standfield, S.; Rayner, C.K.; Feinle-Bisset, C.; Horowitz, M.; Jones, K.L. Effects of small intestinal glucose on glycaemia, insulinaemia and incretin hormone release are load-dependent in obese subjects. *Int. J. Obes.* **2017**, *41*, 225–232. [CrossRef] [PubMed]
10. Hutchison, A.T.; Feinle-Bisset, C.; Fitzgerald, P.C.; Standfield, S.; Horowitz, M.; Clifton, P.M.; Luscombe-Marsh, N.D. Comparative effects of intraduodenal whey protein hydrolysate on antropyloroduodenal motility, gut hormones, glycemia, appetite, and energy intake in lean and obese men. *Am. J. Clin. Nutr.* **2015**, *102*, 1323–1331. [CrossRef] [PubMed]
11. Overduin, J.; Collet, T.H.; Medic, N.; Henning, E.; Keogh, J.M.; Forsyth, F.; Stephenson, C.; Kanning, M.W.; Ruijschop, R.; Farooqi, I.S.; et al. Failure of sucrose replacement with the non-nutritive sweetener erythritol to alter GLP-1 or PYY release or test meal size in lean or obese people. *Appetite* **2016**, *107*, 596–603. [CrossRef] [PubMed]
12. DeBenedictis, J.N.; Nymo, S.; Ollestad, K.H.; Boyesen, G.A.; Rehfeld, J.F.; Holst, J.J.; Truby, H.; Kulseng, B.; Martins, C. Changes in the Homeostatic Appetite System After Weight Loss Reflect a Normalization Toward a Lower Body Weight. *J. Clin. Endocrinol. Metab* **2020**, *105*, e2538–e2546. [CrossRef] [PubMed]
13. Adam, T.C.; Westerterp-Plantenga, M.S. Glucagon-like peptide-1 release and satiety after a nutrient challenge in normal-weight and obese subjects. *Br. J. Nutr.* **2005**, *93*, 845–851. [CrossRef] [PubMed]
14. Meyer-Gerspach, A.C.; Wolnerhanssen, B.; Beglinger, B.; Nessenius, F.; Napitupulu, M.; Schulte, F.H.; Steinert, R.E.; Beglinger, C. Gastric and intestinal satiation in obese and normal weight healthy people. *Physiol. Behav.* **2014**, *129*, 265–271. [CrossRef]
15. Wolnerhanssen, B.K.; Cajacob, L.; Keller, N.; Doody, A.; Rehfeld, J.F.; Drewe, J.; Peterli, R.; Beglinger, C.; Meyer-Gerspach, A.C. Gut hormone secretion, gastric emptying, and glycemic responses to erythritol and xylitol in lean and obese subjects. *Am. J. Physiol. Endocrinol. Metab.* **2016**, *310*, E1053–E1061. [CrossRef] [PubMed]
16. Aukan, M.I.; Nymo, S.; Haagensli Ollestad, K.; Akersveen Boyesen, G.; DeBenedictis, J.N.; Rehfeld, J.F.; Coutinho, S.; Martins, C. Differences in gastrointestinal hormones and appetite ratings among obesity classes. *Appetite* **2022**, *171*, 105940. [CrossRef] [PubMed]
17. Manell, H.; Staaf, J.; Manukyan, L.; Kristinsson, H.; Cen, J.; Stenlid, R.; Ciba, I.; Forslund, A.; Bergsten, P. Altered Plasma Levels of Glucagon, GLP-1 and Glicentin During OGTT in Adolescents with Obesity and Type 2 Diabetes. *J. Clin. Endocrinol. Metab.* **2016**, *101*, 1181–1189. [CrossRef] [PubMed]
18. Faerch, K.; Torekov, S.S.; Vistisen, D.; Johansen, N.B.; Witte, D.R.; Jonsson, A.; Pedersen, O.; Hansen, T.; Lauritzen, T.; Sandbaek, A.; et al. GLP-1 Response to Oral Glucose Is Reduced in Prediabetes, Screen-Detected Type 2 Diabetes, and Obesity and Influenced by Sex: The ADDITION-PRO Study. *Diabetes* **2015**, *64*, 2513–2525. [CrossRef]
19. Witjaksono, F.; Lukito, W.; Wijaya, A.; Annisa, N.G.; Jutamulia, J.; Nurwidya, F.; Simadibrata, M. The effect of breakfast with different macronutrient composition on PYY, ghrelin, and ad libitum intake 4 h after breakfast in Indonesian obese women. *BMC Res. Notes* **2018**, *11*, 787. [CrossRef] [PubMed]
20. Jorsal, T.; Rhee, N.A.; Pedersen, J.; Wahlgren, C.D.; Mortensen, B.; Jepsen, S.L.; Jelsing, J.; Dalboge, L.S.; Vilmann, P.; Hassan, H.; et al. Enteroendocrine K and L cells in healthy and type 2 diabetic individuals. *Diabetologia* **2018**, *61*, 284–294. [CrossRef] [PubMed]