Research Article

Secretion of Gut Hormones and Expression of Sweet Taste Receptors and Glucose Transporters in a Rat Model of Obesity

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Keywords

Gut hormones · Sweet taste receptors · Obesity

Abstract

Objectives: This study was undertaken to compare gut hormone secretion between high-fat-fed and control rats, and to examine the corresponding changes in the expression of sweet taste receptors and glucose transporters in the small intestine and hypothalamus. **Methods:** Four-week-old male Sprague Dawley rats were fed a standard or high-fat diet for 8 weeks (10 in each group), followed by an oral glucose tolerance test (50% glucose solution, 2 g/kg). Blood was sampled for glucose, insulin, glucagon-like peptide-1 (GLP-1) and polypeptide YY (PYY) assays. One week later, small intestinal and hypothalamic tissue were analyzed for sweet taste receptor and glucose transporter expression by real-time PCR. **Results:** After oral glucose, plasma GLP-1 concentrations were higher in high-fat-fed than standard-fat-fed rats (group × time interaction, $p < 0.01$) with significant differences at $t = 15$ min ($p < 0.01$) and 30 min ($p < 0.05$). Plasma PYY concentrations were lower in high-fat-fed than control rats at $t = 0$, 15 min ($p < 0.05$, respectively) and 120 min ($p < 0.01$). There were no differences in the expression of sweet taste receptors or glucose transporters between high-fat-fed and control rats in the duodenum, ileum, or hypothalamus. **Conclusions:** Changes in GLP-1 and PYY secretion after a high-fat diet appear unrelated to any changes in the expression of sweet taste receptors or glucose transporters. Impaired PYY secretion with high-fat feeding suggests that PYY analogues may provide a potential therapy in the treatment of obesity.

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Introduction

Obesity is a rapidly growing health issue, with almost 90 million obese people in China according to the data published in 2016 [1]. Obesity is often accompanied by insulin resistance and impaired glucose homeostasis, which increase the risk for developing type 2 diabetes and cardiovascular diseases [2].

Signals triggered by nutrients in the gastrointestinal tract, such as the gut peptides, glucagon-like peptide-1 (GLP-1) and polypeptide YY (PYY), play an important role in modulating energy intake [3]. GLP-1 is mainly secreted from L-cells in the ileum and colon, with some contribution from the duodenum and jejunum [4]. GLP-1 slows gastric emptying, reduces appetite, stimulates insulin secretion in a glucose-dependent manner, and suppresses glucagon [5]. PYY is co-secreted from intestinal L-cells with GLP-1 [6]. Obese humans have been reported to have lower postprandial GLP-1 and PYY levels when compared to lean controls [7]. GLP-1 receptor agonism and PYY additively reduce food intake and body weight in dietary obese rats and hamsters, respectively [8, 9]. It has also been reported that PYY and GLP-1 have synergistic effects in suppressing appetite and improving insulin resistance [10]. GLP-1 receptor agonists such as liraglutide are now in clinical use for the treatment of obesity [11, 12].

The mechanism of GLP-1 secretion remains controversial. Some studies have suggested that sweet taste receptors (STRs) might be involved in regulating GLP-1 release, as well as glucose absorption [13]. The major pathway for sweet taste transduction in the small intestine has been identified, and involves T1R2/T1R3, the taste-selective $G\alpha$ subunit (α -gustducin), the phospholipase C- β 2, and the inositol 1,4,5-triphosphate receptor, type 3 [14]. Recent studies showed that these STRs and taste signaling elements are expressed in the L-cells along with GLP-1 [15]. The STR blocker, lactisole, attenuated both GLP-1 and PYY secretion in response to intestinal glucose infusion in humans [16, 17]. In animal studies, STRs regulate glucose absorption by increasing mRNA expression of the sodium-dependent glucose co-transporter 1 (SGLT-1) and glucose transporter 2 (GLUT-2) [18, 19].

In the physiological setting, STR activation in hypothalamic neurons [20] and tanycytes [21] contributes to glucose sensing. Taste activity in response to sucrose was increased in the central nervous system, and T1R3 expression was decreased in circumvallate taste buds of dietary obese rats [22]. In mice, obesity was associated with reduced expression of STRs in the brainstem and hypothalamus as well as the duodenum [23]. Patients with morbid obesity had an increased expression of SGLT-1 and reduced expression of STRs in the duodenum [24]. The regulatory function of T1R2/T1R3 makes the STR system a potential molecular therapeutic target for obesity. However, there are few data about obesity-related changes in STR expression in the ileum, where L-cells are predominantly located.

This study aimed to examine gut hormone secretion, as well as expression of sweet taste molecules and glucose transporters in the small intestine and hypothalamus, in high-fat-fed and control rats.

Materials and Methods

Animals and Experimental Design

Four-week-old male Sprague Dawley rats (135–216 g; purchased from Shanghai Laboratory Animal Center, Chinese Academy of Sciences) were kept with constant temperature ($22 \pm 1^\circ\text{C}$) and humidity ($55 \pm 5\%$) in a 12-h/12-h light/dark cycle. Rats were divided into two groups ($n = 10$ each). Control rats had access to chow ad libitum (10% fat, 22% protein, and 68% carbohydrate). High-fat-fed rats had ad libitum access to a diet containing 49% fat,

21% protein, and 30% carbohydrate (Trophic Animal Feed High-tech Co., Ltd., China). Food intake and body weight were assessed each week, and at 8 weeks an oral glucose tolerance test was performed after an overnight fast (16 h, 4:00 p.m. to 8:00 a.m.) by administering 2 g/kg 50% D-glucose (China Otsuka Pharmaceutical Co., Ltd.). At 0, 15, 30, 60, and 120 min after glucose administration, blood samples were collected from the orbital venous plexus into tubes containing EDTA (6 µmol/L) and aprotinin (500 kIU/L). Plasma was separated by centrifugation at 3,000 rpm for 15 min and stored at –80 °C for subsequent hormone assays. At the same time points, blood was sampled from the tail vein, and blood glucose concentrations were measured immediately using a glucometer (Accu-Chek, Roche, Switzerland). One week later, all animals were euthanized at 10:00 a.m. by exsanguination under anesthesia with chloral hydrate (0.4 mL per 100 g), and duodenal, ileal, and hypothalamic tissues were collected and stored at –80 °C for later analysis. All experiments conformed to Institutional Animal Care and Use guidelines with ethical review permissions.

Plasma Insulin, GLP-1 and PYY Measurements

Plasma insulin was measured by ELISA (Shibayagi, Gunma, Japan), with an intra-assay coefficient of variation of 2.77%. Plasma total GLP-1 was measured by ELISA (Crystal Chem, Downers Grove, IL, USA) with an intra-assay coefficient of variation of 4.96%. Total PYY was measured by rat ELISA (Crystal Chem, Downers Grove, IL, USA), with an intra-assay coefficient of variation of 4.96%. No cross-reactivity with rat NPY, GLP-1 [7–36], NH2, GLP-1 [1–37], or GLP-2 was observed.

RNA Isolation and Real-Time PCR

Duodenal, ileal, and hypothalamic specimens were lysed using Trizol Reagent (Invitrogen, USA). Total RNA was extracted using the phenol-chloroform method. Eluted RNA was diluted 1:50 in DEPC water and quantified in triplicate by spectrophotometry (260 nm) using a NanoDrop 2000c instrument (Thermo Scientific, USA). The procedure of reverse transcription was prepared by using a PrimeScript RT reagent kit (TaKaRa, Japan) according to the manufacturer's protocol. Quantitative RT-PCR was performed with a Primer version 5.0 software (Sangon Biotech Shanghai Co., Ltd.), using a SYBR Green Real-Time PCR Master Mix (TaKaRa, Japan), according to the manufacturer's instructions. Sequences of primers used for quantitative RT-PCR were as follows: T1R2, 5'-TTCTCATGCTTCTGCCGACAG-3' and 5'-GCC-ATCTTGAAGACACACACGA-3'; T1R3, 5'-AACAACCAATGGCTCACCTCC-3' and 5'-AAAGCCAT-CAAGTACCAGGCAC-3'; α-gustducin, 5'-GCGATCCAGGAATTCAAGCCT-3' and 5'-GATACCAG-TGGTTTTTCACCCGG-3'; TRPM5, 5'-TGGCCCTCGATCTTTTCTCAG-3' and 5'-AATGCTTGACAC-CATCATGG-3'; SGLT-1, 5'-ATTGGAATCTCCCGTATG-3' and 5'-ATGACGAAGAGGATGATG-3'; GLUT-2, 5'-ATTACCGACAGCCCATCC-3' and 5'-TCCACAAGCAGCACAGAG-3'; GAPDH, 5'-ATC-ACTGCCACCCAGAAG-3' and 5'-TCCACGACGGACACATTG-3'. The relative amount of each transcript was normalized to the amount of GAPDH transcript in the same cDNA.

Statistical Analysis

Differences in blood glucose and plasma insulin, GLP-1 and PYY concentrations between control and high-fat diet groups were assessed by repeated-measures ANOVA with treatment and time as factors. In addition, the differences in the copy numbers of intestinal STR and glucose transporter transcripts between the groups were compared using one-way ANOVA. Analyses were performed using GraphPad Prism statistical software, version 6 (GraphPad Software). Significance was accepted at $p < 0.05$; data are presented as mean ± standard error.

Fig. 1. Blood glucose and plasma concentrations of insulin, GLP-1, and PYY after the glucose load (2 g/kg glucose dissolved in water) in the high-fat-fed and the control group. Data are presented as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$.

Results

All rats tolerated the procedures well. Body weights of the high-fat diet group were 520.1 ± 9.7 g and those of the control group were 447.1 ± 6.9 g.

Blood Glucose Concentrations

There was no difference in fasting blood glucose between the high-fat and control groups. Blood glucose concentrations (Fig. 1A) increased in both to a peak at 15 min after glucose administration, without any difference between them.

Plasma Insulin Concentrations

Fasting plasma insulin concentrations (Fig. 1B) were numerically but not statistically higher in the high-fat group than the controls. After glucose administration, insulin concentrations increased markedly at $t = 15$ min in both groups and were greater in the high-fat than the control group at $t = 15, 60$ and 120 min (group $\times$ time interaction, $p < 0.01$).

Fig. 2. Relative expression levels of sweet taste molecules T1R2, T1R3, the G-protein α -gustducin, the transient receptor-potential ion channel (TRPM5), and glucose transporters (SGLT-1 and GLUT-2) in the duodenum, ileum, and hypothalamus in control (CON) and high-fat groups (HF). Data are presented as mean $\pm$ SEM.

Plasma GLP-1 Concentrations

Fasting plasma GLP-1 (Fig. 1C) did not differ between the groups. After the glucose load, there was a marked increase in plasma GLP-1 at $t = 15$ min in both groups, with substantially higher GLP-1 concentrations in the high-fat group (group $\times$ time interaction) at $t = 15$ min ($p < 0.01$) and 30 min ($p < 0.05$).

Plasma PYY Concentrations

Fasting plasma PYY concentrations (Fig. 1D) were lower in high-fat-fed rats than the controls ($p < 0.05$). Plasma PYY concentrations in response to the glucose load were lower in the high-fat group than controls at $t = 15$ and 120 min (group $\times$ time interaction, $p < 0.05$ and $p < 0.01$).

Relative Transcript Levels of STRs and Glucose Transporters in the Small Intestine and Hypothalamus

Expression of T1R2 (Fig. 2A), T1R3 (Fig. 2B), α -gustducin (Fig. 2C), TRPM5 (Fig. 2D), SGLT-1 (Fig. 2E), and GLUT-2 (Fig. 2F) transcripts did not differ between the high-fat and the control group, in either the duodenum (a), ileum (b), or hypothalamus (c).

Discussion

The present study showed that plasma PYY levels were reduced in high-fat-fed rats, while those of GLP-1 were increased, when compared to controls. Patients with morbid obesity are reported to exhibit less GLP-1 secretion following glucose ingestion than lean subjects, while diet restriction or gastric bypass surgery in these patients are associated with enhanced GLP-1 concentrations [25]. The rate of gastric emptying is a major determinant of GLP-1 secretion [7] and has been reported to be faster in overweight and mild obesity [26]. Higher GLP-1 concentrations in obesity might therefore be secondary to an increased rate of gastrointestinal transit. The increased glucose-stimulated insulin release in pre-obese rats may be due to the increased GLP-1 release as a result of its incretin action.

It has previously been reported that fasting and postprandial PYY levels are decreased in obese subjects, compared to lean subjects [27]. Our previous study demonstrated that PYY levels negatively correlated with HOMA-IR and BMI in patients with polycystic ovary syndrome [28]. In the current study, we observed that PYY concentrations were lower in high-fat-fed rats than controls, during both fasting and after the glucose load, which is consistent with these reports. The dissimilarity of PYY and GLP-1 secretion patterns after the high-fat diet might also be explained by differences in L-cells between the proximal and distal small intestine [6]. L-cells in the distal small intestine appear to have a greater capacity to secrete PYY than GLP-1 [6]. In this site, short-chain fatty acids (SCFAs) produced by the microbiota, increase plasma PYY, but not GLP-1 levels, both in the fasted and fed states [29]. A high-fat diet produces less SCFAs than a high-carbohydrate diet [30]. Furthermore, PYY and GLP-1 can be stored in different vesicles in L-cells which can explain their differential release [31]. The fact that obese and lean subjects appear equally sensitive to the effect of exogenous PYY3–36 to suppress food intake [27] suggests the potential utility of PYY as a therapeutic target for obesity in the future.

Certain “taste” receptors expressed in the gut drive hormone release in response to nutrients. Sensing of amino acids by the calcium-sensing receptor triggers GLP-1 secretion [32]. GLP-1 secretion on exposure to fat depends on the G protein-coupled receptor, GPR120 while SCFAs are sensing by GPR43 and GPR41 to regulate PYY release [33, 34]. The STR, T1R2/T1R3, detects intestinal monosaccharides to elicit secretion of GLP-1 and PYY [16].

Studies in obese mice reported that T1R2 and T1R3 expression was low and that this was associated with basal insulin hypersecretion [35]. We did not show any differences in the expression of STRs or associated signaling pathway molecules between high-fat-fed and control groups. STR expression in the gut is regulated by luminal glucose exposure and blood glucose concentrations [36]. Fasting and postprandial blood glucose levels and intestinal glucose exposure did not differ between the two groups in our study. The fact that PYY and GLP-1 secretion were altered in response to the high-fat diet in the absence of any changes in intestinal STR or glucose transporter expression indicates that the latter are unlikely to be major determinants of changes in secretion of these gut hormones in this model of obesity. Some studies have suggested that the function of glucose transporters is more closely related to the secretion of the incretin hormones than the STR system. For example, in morbidly obese humans, duodenal expression of SGLT-1, but not STRs, was increased, and was associated with accelerated proximal intestinal glucose absorption [24]. This would increase GIP secretion at the expense of more distal hormones like PYY and (in humans) GLP-1. In rats, GIP is a stimulus for GLP-1 secretion, but we did not measure GIP in our study. The most studied plant-derived inhibitory compounds towards STRs are lactisole and gurmardin [37]. The role of intestinal STRs in the pathogenesis of obesity could be explored further by the use of specific inhibitors.

This study has several limitations. Firstly, we did not observe protein expression and/or activity of the STR components and glucose transporters in the study. Secondly, average body weight reached in the high-fat-fed group was only modestly higher than that in controls, and greater effects may have been induced by the larger difference in body weight. Moreover, we collected whole-wall tissue for intestinal samples rather than isolating enterocytes by scraping or simple shaking enriches samples, which might affect the results. Thirdly, we cannot be certain that the intervention was long enough to induce significant changes in sweet molecule expression in either the intestine or the hypothalamus. Lastly, the glucose load was administered into the stomach rather than the small intestine, so we cannot exclude differences in the rate of gastric emptying as a confounding variable.

In conclusion, our study did not find any differences in sweet taste or glucose transporter molecule expression in the ileum or duodenum between high-fat-fed and control rats, despite there being increased GLP-1 but impaired PYY secretion. A PYY analogue has been tested which causes profound feeding suppression in mice well beyond that of PYY [38]. The latter suggests that PYY analogues might be a potential intervention in the treatment of obesity.

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Statement of Ethics

All experiments conformed to Institutional Animal Care and Use guidelines with ethical review permissions.

Disclosure Statement

The authors declare no conflict of interest.

Author Contributions

R.L.F. contributed to experimental work and analyzed data. C.Q. contributed to the acquisition of data, experimental work and wrote the manuscript. L.Y.L., Q.J.L., and Y.Q.J. contributed to the study design and critical review of the article. S.X.L., W.L., and C.K.R. contributed to the study design and approved the final version. J.M. contributed to the study design, drafting of the article, analysis of data, and approved the final version.

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