The role of the gut sweet taste receptor in regulating GLP-1, PYY, and CCK release in humans

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Gerspach AC, Steinert RE, Schönemberger L, Graber-Maier A, Beglinger C. The role of the gut sweet taste receptor in regulating GLP-1, PYY, and CCK release in humans. Am J Physiol Endocrinol Metab 301: E317–E325, 2011. First published May 3, 2011; doi:10.1152/ajpendo.00077.2011.—The recent identification of sweet taste receptors in the gastrointestinal tract has important implications in the control of food intake and glucose homeostasis. Lactisole can inhibit the sweet taste receptor T1R2/T1R3. The objective was to use lactisole as a probe to investigate the physiological role of T1R2/T1R3 by assessing the effect of T1R2/T1R3 blockade on GLP-1, PYY, and CCK release in response to intragastric administration of nutrients or intraduodenal perfusion of nutrients. The study was performed as a randomized, double-blind, placebo-controlled crossover study that included 35 healthy subjects. In part I, subjects received intragastrically 75 g of sucrose in 300 ml of water or 500 ml of a mixed liquid meal with or without lactisole. In part II, subjects received an intraduodenal perfusion of glucose (29.3 g glucose/100 ml; rate: 2.5 ml/min for 180 min) or a mixed liquid meal (same rate) with or without lactisole. The results were that lactisole induced a significant reduction in GLP-1 and PYY but not CCK secretion in both the intragastric and the intraduodenal glucose-stimulated parts (P < 0.05). Comparison of the inhibitory effect of lactisole showed a significantly greater suppression of the hormone response in the intragastric part (P = 0.023), and lactisole had no effect on liquid meal-stimulated parameters. We conclude that T1R2/T1R3 is involved in glucose-dependent secretion of satiation peptides. However, the results of the liquid meal-stimulated parts show that the receptor alone is not responsible for peptide secretion.

Enteroendocrine cells in the human gut sense chemical components of ingested food and secrete a number of gastrointestinal satiation peptides, including glucagon-like peptide 1 (GLP-1), peptide tyrosine-tyrosine (PYY), and cholecystokinin (CCK) (41). All of them have been demonstrated to influence gastric emptying, increase satiety, and reduce food intake (8, 13, 18, 23, 30, 37). Recently, it has been shown that G protein-coupled receptors that sense chemical components of food on the tongue, including the sweet taste receptor (T1R2/T1R3) as well as key elements like α-gustducin, phospholipase Cβ2 (PLCβ2), and transient receptor potential channel type 5, also exist in enteroendocrine cells of the gut (2, 10, 16, 31).

It is known that glucose is an activator for the sweet taste receptor on the tongue; in addition, glucose is a strong stimulus of the secretion of gastrointestinal peptides. Because the sweet taste receptor system in the gut could be involved in the secretion of gastrointestinal peptides, lactisole, the sodium salt of 2-(4-methoxyphenoxy)-propionic acid, should attenuate the glucose-stimulated peptide secretion. In vivo lactisole suppresses the sweet taste perception on the tongue; the inhibitory effect is specific to humans and other primates. Furthermore, in vitro, lactisole antagonizes the effects of sucralose-stimulated GLP-1 release from human enteroendocrine (NCI-H716) cells (16, 17, 38).

In a preliminary study, we were able to show that in healthy humans the secretion of GLP-1 and PYY in response to glucose was reduced by lactisole (40). These data suggest that lactisole could be an excellent tool to investigate the regulatory role of the sweet receptor’s dependent physiological functions in humans.

The objectives were to use lactisole as a probe to investigate the physiological role of the sweet taste receptor by assessing the effect of the sweet receptor blockade on GLP-1, PYY, and CCK release in response to intragastric administration of nutrients or intraduodenal perfusion of nutrients. Furthermore, we were interested to determine the consequences on glucose homeostasis and the effect of sweet taste receptor blockade on appetite perceptions and on gastric emptying rates.

Methods

Subjects

Thirty-five volunteers (20 males and 15 females; mean age: 24 ± 0.4 yr, range 19–30 yr) participated in the study. All subjects were healthy, with weight within the normal range in relation to age, sex, and height (mean BMI: 22.3 ± 0.3 kg/m2, range 19.0–25.9 kg/m2). The protocol was submitted to and approved by the State Ethics Committee of Basel, Switzerland, and the study was carried out in accordance with the principles of the Declaration of Helsinki. Each subject gave written informed consent for the study. Before acceptance, each participant was required to complete a screening and medical interview, received a full physical examination, and participated in an initial laboratory screening. The criteria for exclusion were smoking, substance abuse, regular intake of medications (except for oral contraceptives), medical or psychiatric illness, and any abnormalities detected upon physical examination or laboratory screening. None of the subjects had a history of gastrointestinal disorders, food allergies, or dietary restrictions. Subjects were instructed to abstain from alcohol, caffeine, and strenuous exercise for 24 h before each treatment.

Experimental Procedure

The study consisted of two experimental parts. Each part was performed as a randomized, double-blind, placebo-controlled crossover study, with each subject studied on two (part I) or five (part II) occasions ≥3 days apart. Subjects’ food intake on the preceding day of each study day was standardized; they consumed a restricted simple-carbohydrate standard dinner before 8 PM and fasted from 10...
of 10 subjects was labeled with 50 mg of [13C]sodium acetate for determination of gastric emptying rate.

In a first series, 26 subjects (13 males and 13 females) received an intragastric infusion of 75 g of glucose alone (300 kcal) or glucose together with 450 ppm lactisole (45 mg/100 ml) dissolved in 300 ml of tap water within 2 min (t = 0–2 min). In addition, the test solution of 10 subjects was labeled with 50 mg of [13C]sodium acetate for determination of gastric emptying rate. In a second series, 16 subjects (8 males and 8 females) received an intragastric infusion of a complex liquid meal (500 ml of Ensure Plus; 17% protein, 30% fat, and 53% carbohydrate; caloric load: 600 kcal) with 450 ppm (45 mg/100 ml) lactisole dissolved. All test solutions were labeled with 50 mg of [13C]sodium acetate for determination of gastric emptying. The placebo treatment was the test solution without lactisole.

The chosen doses of lactisole derive from previous experiments (35, 40). The intragastric infusions were freshly prepared each morning of the study and were at room temperature when administered. The feeding tube was removed immediately after the infusion was completed. At regular time intervals, 10-ml blood samples were collected on ice into tubes containing EDTA (6 μmol/l), aprotinin (500 kIU/ml), and a dipeptidyl peptidase IV inhibitor. After centrifugation (3,000 rpm, 10 min at 4°C), plasma samples were processed into different aliquots and kept frozen at −70°C until analysis. Immediately after each blood collection, appetite perceptions such as feelings of hunger, prospective food consumption, fullness, and satiety were recorded.

For determination of the gastric emptying rates, end-expiratory breath samples were taken at fixed time intervals after instillation of the test solution. Vital signs (blood pressure, heart rate) were measured before and after each study day.

Assessment of Gastric Emptying

Gastric emptying rate was determined using a [13C]sodium acetate breath test. This test is an accurate, noninvasive, simple method, without radiation exposure, and represents a reliable alternative to scintigraphy, the gold standard for measuring gastric emptying (4, 34). Test solutions were labeled with 50 mg of [13C]sodium acetate, which is rapidly absorbed in the duodenum, transported to the liver, and metabolized to [12CO2] (22). Subjects were asked to exhale through a mouthpiece to collect an end-expiratory breath sample into a 100-ml foil bag. The [13CO2] breath content was then determined by nondispersive infrared spectroscopy using an isotope ratio mass spectrophotometer (IRIS; Wagner Analysen Technik). The [13CO2]/[12CO2] ratio in progress of time was used as a parameter for gastric emptying. Mathematical analysis were performed according to the methods described by Sanaka et al. (34).

Hormones

GLP-1 was measured with a commercially available ELISA kit (Millipore, Billerica, MA). This kit is for nonradioactive quantification of GLP-1(7–36) in serum and EDTA plasma samples; it is highly specific and does not detect other forms of GLP-1. The lowest level of GLP-1 that can be detected by this assay is 0.5 pmol/l when a 100-μl plasma sample is used. Prior to measurements, GLP-1 was extracted from 1 ml of plasma by using a reversed solid-phase extraction (C18-silica cartridges: Waters, Baden-Dättwil, Switzerland).

PYY was measured with a commercially available radioimmunoassay kit (Linco Research, St. Charles, MO). The anti-PYY antibody used in this kit is raised in guinea pigs and displays 100% cross-reactivity with human PYY1–36 and human PYY3–36 but no cross-reactivity with human pancreatic polypeptide, neuropeptide Y, or unrelated peptides such as leptin and ghrelin. The intra- and interassay coefficients of variation for this assay are <9.4 and 8.5%, respec-
tively. The lowest level of PYY that can be detected by this assay is 10 pg/ml when a 100-μl plasma sample is used.

CCK concentrations were measured by a commercially available radioimmunoassay kit (Euro-Diagnostica, Malmö, Sweden). This kit is for assay of CCK in plasma by using an antiserum raised against sulfated CCK-8 NH₂ terminally conjugated to bovine albumin. The antiserum displays 100% cross-reactivity with CCK-8 sulphate but no relevant cross-reactivity with sulfated gastrin. The intra- and interassay coefficients of variation for this assay are <5.5 and 13.7%, respectively. The lowest detectable concentration is 0.3 pmol/l when a 200-μl plasma sample is used. Prior to measurements, CCK was extracted from 1 ml of plasma by using an ethanol extraction method.

Insulin was measured with a commercially available radioimmunoassay (CIS Bio International, Bagnols, France). This kit is for quantitative determination of insulin in human serum and plasma (EDTA). It is highly specific for insulin and shows no cross-reactivity with other peptides, e.g., C-peptide or glucagon. The intra- and interassay coefficients of variation for this assay are <12.2 and 9.0%, respectively. The lowest level of insulin that can be detected by this assay is 4.6 μU/ml.

Plasma glucose concentration was measured by a commercially available glucose oxidase method (Bayer Consumer Care, Basel, Switzerland). This method is highly specific for measurement of glucose in serum or plasma. The lowest level of glucose that can be detected by this assay is 0.6 mmol/l.

Statistical Analysis

Descriptive statistics were used for demographic variables such as age, weight, height, and BMI.

Hormone and glucose profiles were analyzed by calculating pharmacodynamic parameters [area under the concentration-time curve (AUC), ΔAUC, maximal plasma concentration (Cₘₐₓ), and time to maximal plasma concentration (Tₘₐₓ)]. The parameters were tested for normality by the Shapiro-Wilk test. To test for significant differences between the treatment groups within parts I and II, AUC, Cₘₐₓ, and Tₘₐₓ were compared using Student’s paired t-test. To test for significant differences between parts I (intragastric infusions) and II (intraduodenal perfusions), ΔAUC were assessed using Student’s unpaired t-test.

VAS ratings were analyzed statistically by calculating AUC (0–120 min) from baseline. These data were compared between the treatments using the nonparametric Wilcoxon’s signed-rank test due to high variability and nonnormal distribution (Shapiro-Wilk test).

All statistical analysis was done using the statistical software package SPSS for Windows Version 14.0 (SPSS, Chicago, IL). Values were reported as means ± SE. All tests were two-tailed, with P ≤ 0.05 considered statistically significant.

RESULTS

Effect of Sweet Taste Receptor Blockade in Response to Intragastric Nutrients

GLP-1, PYY, and CCK. Lactisole induced a reduction in intragastric glucose-stimulated secretion of GLP-1 and PYY (24.3 ± 7.7 and 15.5 ± 6.1%, respectively; Fig. 1, A and B). AUCs were significantly decreased by lactisole compared with the administration of glucose alone (P = 0.007 and 0.012;
Table 1. Effect of lactisole (450 ppm) on intragastric glucose-stimulated secretion of GLP-1, PYY, insulin and glucose in healthy subjects

<table>
<thead>
<tr>
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<th>Glucose Alone (Placebo)</th>
<th>Glucose + 450 ppm Lactisole</th>
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<tr>
<td><strong>GLP-1</strong></td>
<td></td>
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<tr>
<td>AUC (0–120 min),</td>
<td>489.2 ± 76.3</td>
<td>267.3 ± 29.0 (P = 0.007)</td>
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<tr>
<td>pmol·min⁻¹·l⁻¹</td>
<td>12.2 ± 2.3</td>
<td>5.3 ± 0.8 (P = 0.007)</td>
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<tr>
<td>Cmax, pg/ml</td>
<td>173.4 ± 17.2</td>
<td>128.2 ± 7.8 (P = 0.012)</td>
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<tr>
<td><strong>PYY</strong></td>
<td></td>
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<tr>
<td>AUC (0–120 min),</td>
<td>17,488.4 ± 1,637.8</td>
<td>13,170.5 ± 787.7 (P = 0.0012)</td>
</tr>
<tr>
<td>pg·min⁻¹·ml⁻¹</td>
<td>118.0 ± 8.0</td>
<td>100.4 ± 7.0 (P = 0.048)</td>
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<tr>
<td>Cmax, (0–30 min),</td>
<td>759.9 ± 24.4</td>
<td>830.6 ± 34.3 (P = 0.029)</td>
</tr>
<tr>
<td>μU/ml</td>
<td>9.1 ± 0.4</td>
<td>9.5 ± 0.4 (NS)</td>
</tr>
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Data are expressed as means ± SE; n = 26. GLP-1, glucagon-like peptide-1; PYY, peptide tyrosine-tyrosine; AUC, area under the concentration-time curve; Cmax, maximum plasma concentration; NS, not statistically significant vs. glucose alone. P values are given in parentheses and represent comparisons vs. glucose alone (placebo). P ≤ 0.05, statistically significant difference vs. glucose alone.

In contrast, lactisole showed no significant effect on intragastrically administered mixed liquid meal-stimulated secretions of GLP-1 and PYY (Fig. 1, D and E). Plasma CCK levels were not affected by lactisole either after intragastric glucose or after mixed liquid meal administration (Fig. 1, C and E).

Glucose and insulin. The AUCs for plasma glucose were increased significantly by lactisole when glucose was intragastrically infused (P = 0.029; Fig. 2A and Table 1).

Plasma insulin was reduced significantly by lactisole in the first 30 min (Cmax; P ≤ 0.05), although no significant differences were seen in the later time course of insulin compared with administration of glucose alone (Fig. 2B and Table 1).

In contrast, neither plasma glucose levels nor insulin release was affected by intragastric liquid meal administration (Fig. 2, C and D).

Appetite perceptions. We observed a reduction in fullness by lactisole when glucose was intragastrically infused; however, the effects did not reach the level of statistical significance (Fig. 3A). In contrast, no effect was observed after liquid meal administration (Fig. 3B).

Gastric emptying. The rate of gastric emptying was not affected by lactisole either after glucose or after mixed liquid meal administration (Fig. 4).

Effect of Sweet Taste Receptor Blockade in Response to Intraduodenal Nutrients

GLP-1, PYY, and CCK. During intraduodenal infusions of glucose, lactisole induced a reduction (11.9 ± 4.2%) in GLP-1 secretion; AUC (0–120 min) for GLP-1 was significantly decreased by lactisole compared with the administration of glucose alone (P = 0.031; Fig. 5A). In contrast, PYY and CCK secretions were not significantly reduced (Fig. 5B; data not shown for CCK). In parallel to the intragastric part, lactisole showed no significant effect on intraduodenal liquid meal-stimulated secretions of GLP-1 and PYY (Fig. 5, C and D).

Glucose and insulin. Plasma glucose and insulin concentrations were not affected by lactisole when either glucose or the liquid meal was intraduodenally infused (Fig. 6, A–D). However, glucose and insulin levels in the glucose-stimulated part trended toward a glucose/insulin profile that was already observed after administration of glucose (Fig. 2, A and B).

Appetite perceptions. A slight reduction in feelings of fullness was observed when glucose was intraduodenally infused; however, these effects did not reach the level of statistical significance (Fig. 3C). In parallel to the intragastric part, lactisole showed no significant effect on intraduodenal liquid meal-stimulated secretions of GLP-1 and PYY (Fig. 5, C and D).
tric part, no effect in fullness was seen during the liquid meal infusion (Fig. 3D).

Comparison of the Intragastric and Intraduodenal Inhibitory Effect of Lactisole on Peptide Secretion

The inhibitory effect of lactisole on GLP-1 secretion was significantly greater after intragastric administration of glucose than after intraduodenal perfusion of glucose ($P = 0.023$; Fig. 7).

No differences in the inhibitory effect of lactisole were seen between the intragastric vs. intraduodenal administration of the mixed liquid meal.

DISCUSSION

The recent identification of the sweet taste receptor T1R2/T1R3 and the detection of $\alpha$-gustducin, PLC $\beta_2$, and transient receptor potential channel type 5 in enteroendocrine cells of the human gut let one anticipate a taste system in the gastrointestinal tract comparable with that in the mouth (2, 10, 31). The discovery of such a “new” receptor system raises the question of whether and how this system contributes to glucose sensing and metabolism. By defining activators and inhibitors of this system, we sought to define the importance of sweet taste receptors in the secretion of satiation peptides and appetite control.

In previous studies in humans, it was shown that glucose acts as an activator of this sweet taste receptor system with regard to peptide secretion, whereas artificial sweeteners showed no such effect (16, 21, 39). Lactisole, the sodium salt of 2-(4-methoxyphenoxy)-propionic acid, is a potential inhibitor of this receptor system. In vitro, lactisole has been shown to inhibit the effects of sucralose-stimulated GLP-1 release from human enteroendocrine (NCI-H16) cells (16). In vivo, it suppresses the sweet taste on the tongue; the inhibition is observed only when sweeteners and lactisole are mixed prior to tasting and appears to be a competitive inhibition (35). Lactisole inhibits the T1R2/T1R3 human sweet taste receptor by binding to the transmembrane domain of hT1R3 (17). In a pilot study, we were able to show that the secretion of GLP-1 and PYY in response to glucose was reduced by lactisole in healthy human subjects (40). These data suggest that lactisole could be an excellent tool to investigate the regulatory role of the gut-expressed sweet receptor’s dependent physiological functions in humans.

Two different approaches were used to establish the role of sweet taste receptor blockade on the secretion of gastrointestinal satiation peptides, including GLP-1, PYY, and CCK, and the influence on glucose homeostasis: 1) an intragastric administration of two liquid meals (glucose and a mixed meal) with and without lactisole and 2) intraduodenal perfusion of the same meals, in which for both the effect of lactisole on glucose- and liquid meal-stimulated secretion of satiation peptides was examined.

The results can be summarized as follows. 1) Lactisole induced a significant reduction in GLP-1 and PYY but not CCK secretion in the intragastric glucose-stimulated part ($P = 0.007$ and 0.012); as a consequence, plasma insulin levels were significantly decreased in the early postprandial state ($C_{\text{max}}$; $P \leq 0.05$), and subsequently, glucose levels increased significantly ($P = 0.029$). Appetite perceptions showed a trend for reduced feelings of fullness. 2) Lactisole induced a smaller, albeit still significant ($P = 0.031$), reduction in GLP-1 secretion in the intraduodenal glucose-stimulated part; however, PYY and CCK secretions were not significantly reduced. 3) Comparison of the inhibitory effect of lactisole on the secretion of GLP-1 in response to intragastric vs. intraduodenal administration of glucose showed a significantly greater suppression of the hormone response in the intragastric part ($P = 0.023$). 4) Lactisole had no effect on
mixed liquid meal-stimulated parameters in either the intragastric or the intraduodenal part. 5) The gastric emptying rates were not affected by lactisole with either glucose or mixed liquid meal stimulation.

The results are in line with previous in vitro and in vivo animal studies (16, 17) showing that lactisole is an effective antagonist of the sweet taste receptor system to glucose stimulation. In a previous study, we established an inhibition of lactisole on glucose-stimulated GLP-1 release in healthy male subjects (40). The current results confirm these results and show again that blockade of the sweet taste receptor in the human gut not only significantly reduces the secretion of GLP-1 but also reduces PYY release. Previous in vitro or animal studies have not suggested such an effect for PYY. Therefore, in addition to GLP-1, PYY secretion must be taken into account whenever the sweet taste receptor system in the human gut is evaluated. Our results confirm the findings that the release of CCK is, beside fats and proteins, also stimulated by the presence of glucose in the proximal small intestine (19, 20). The lack of effect of lactisole on CCK release let us assume that glucose-induced CCK secretion is not mediated by the sweet taste receptor T1R2/T1R3 and that other glucose-sensing receptors must be involved.

The current results were to a certain extent surprising, since we did not anticipate a smaller effect of sweet taste receptor blockade in the intraduodenal perfusion studies. Interaction of nutrients with the small intestine plays an important role in the regulation of glucose homeostasis. Furthermore, the presence of glucose in the small intestine is a well-established stimulus for GLP-1 secretion, leading (together with GIP) to glucose-dependent insulin secretion from the β-cells and a feedback that regulates gastric emptying (36). Direct exposure of carbohydrate to the mucosa of the small intestine appears to be an essential requirement for GLP-1 secretion (6), and the magnitude is dependent on the rate of duodenal glucose entry (27, 29). Although the sweet receptor subunit T1R3 has been shown to be present in both the human stomach and the small intestine, it is expressed predominantly in duodenum and jejunum, and furthermore, the expression of the sweet receptor subunit T1R2 was not found in the stomach (2, 14, 44). Based
on these findings, we would infer a greater effect of sweet receptor blockade after duodenal meal perfusion. Since this was not the case, an interaction of the stomach with signals from the small intestine is a more likely interpretation.

Furthermore, the observed smaller effect of lactisole on the release of satiation peptides in the intraduodenal part suggests a relevant contribution of the stomach in the regulation of these hormones. One assumption is that the sweet receptor subunit T1R3 in the stomach plays a role in detection of nutrients, which in turn initiates a hormonal or neural cascade pathway that is crucial in the secretion of satiation peptides (9, 14). Another potential mechanism could be the influence of gastric distension. In the intragastric study glucose was given as bolus within 2 min, whereas in the intraduodenal study glucose was perfused continuously over 3 h. Therefore, in the intragastric study, gastric distension was increased, which may have an influence on secretion of satiation peptides and subsequently on the inhibitory effect of lactisole. However, previous studies showed that satiation peptides like CCK and PYY were not altered by mechanical gastric distension (28). A further explanation could be that the gastric emptying rates had an influence on the effectiveness of lactisole. Although several investigators have suggested that a key mechanism of GLP-1 with respect to glucose control is based on its effect on gastric emptying (24), this hypothesis is based on the results of studies using exogenous administration of GLP-1. In the present study, we document an identical pattern of postprandial gastric emptying with and without lactisole, suggesting that endogenous GLP-1 has no detectable effect on the rate of passage of glucose from the stomach to the duodenum. The lack of effect of lactisole to alter $^{13}$CO$_2$ appearance in the breath is similar to what has been reported previously in studies with GLP-1 receptor blockade in healthy human subjects, in patients with type 2 diabetes mellitus, and in nonhuman primates given liquid glucose solutions (5, 32, 33). In the present study, we show that blocking the sweet receptor, which induced an attenuated GLP-1 response, has no effect on gastric emptying rates; our data stand against an important physiological role for GLP-1 in the regulation of prandial gastric emptying in humans. Not all data are consistent with this conclusion. Deane et al. (7) recently published evidence that endogenous GLP-1 delays gastric emptying in healthy subjects after a solid carbohydrate meal. However, these findings could not be confirmed by Nicolaus et al. (26), who reported that blockade of the GLP-1 receptor by the specific receptor antagonist Ex-(9–39) had no effect on gastric emptying of a mixed semisolid oral meal. Both investigators used scintigraphy, the gold standard for measuring gastric emptying. The reasons for these discrepancies remain unclear, but the available evidence suggests that changes in gastric emptying mediated by GLP-1 probably do
not play a major role in the regulation of glucose homeostasis in humans.

In contrast to our expectations, lactisole had no effect on parameters stimulated by a mixed liquid meal in either the intragastric or intraduodenal part. Besides glucose, the liquid meal also consists of proteins, fats, and other complex carbohydrates. The lack of effect of lactisole suggests that these nutrients induce the release of satiation peptides via other mechanisms; more importantly, these mechanisms seem to outweigh the effect of sweet receptor blockade. This raises the question of the physiological importance of the sweet taste receptor system in regulating GLP-1 release and associated functions. Long-chain fatty acids, apart from glucose, are also potent luminal secretagogues for GLP-1 release (1). Thus, the fast response to glucose is based on tasting and activation of the sweet receptor system, whereas the effects of a mixed meal are also mediated by lipids and perhaps proteins. A potential mechanism by which lipids stimulate the secretion of gastrointestinal satiation peptides is through activation of GPR120, a specific receptor for medium- and long-chain free fatty acids (15, 42). In addition, there are several receptors that possibly act as amino acid sensors, like T1R1/T1R3, the extracellular Ca\(^{2+}\)-sensing receptor, or the Na\(^{+}\)-coupled neutral amino acid transporter 2 (12, 25, 43, 45). Finally, additional sensing mechanisms for carbohydrates have been proposed, which are different from the sweet taste receptor T1R2/T1R3 (46). Therefore, the multiplicity of different receptors suggests that the sweet taste receptor T1R2/T1R3 alone is not responsible in the regulation of GLP-1 release and associated functions.

We have not measured whether the presence of lactisole in the duodenum affects the expression of T1R3, T1R2, or α-gustducin. Young et al. (44) previously showed that the expression of T1R2 was decreased by jejunal glucose perfusion in mice. These results suggest the existence of a mechanism that can downregulate the sweet taste receptor in the presence of agonists. Whether an antagonist like lactisole has comparable effects on the regulation of receptor expression is not known. If so, the preloading of lactisole in the second part of our study could have resulted in a reduced availability of the receptor to intraduodenal stimuli, which would have affected the secretion of GLP-1 and PYY.

In conclusion, the present results show that the sweet taste receptor system is involved in the secretion of gastrointestinal satiation peptides, with potential effects on glucose homeostasis. The study raises questions with respect to the functional involvement of sweet taste receptors expressed in the stomach and the role of the stomach in the release of satiation peptides. The physiological conclusions of these findings seem to indicate that the sweet taste receptor in the gut is of limited importance and is not alone responsible for peptide release; rather, it is a complex interaction between different receptor mechanisms.

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