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ORIGINAL ARTICLE

Tripeptide gut hormone infusion does not alter food preferences or sweet taste function in volunteers with obesity and prediabetes/diabetes but promotes restraint eating: A secondary analysis of a randomized single-blind placebo-controlled study

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Abstract

Aims: To investigate whether the elevation in postprandial concentrations of the gut hormones glucagon-like peptide-1 (GLP-1), oxyntomodulin (OXM) and peptide YY (PYY) accounts for the beneficial changes in food preferences, sweet taste function and eating behaviour after Roux-en-Y gastric bypass (RYGB).

Materials and methods: This was a secondary analysis of a randomized single-blind study in which we infused GLP-1, OXM, PYY (GOP) or 0.9% saline subcutaneously for 4 weeks in 24 subjects with obesity and prediabetes/diabetes, to replicate their peak postprandial concentrations, as measured at 1 month in a matched RYGB cohort (ClinicalTrials.gov NCT01945840). A 4-day food diary and validated eating behaviour questionnaires were completed. Sweet taste detection was measured using the method of constant stimuli. Correct sucrose identification (corrected hit rates) was recorded, and sweet taste detection thresholds (EC50s: half maximum effective concencration values) were derived from concentration curves. The intensity and consummatory reward value of sweet taste were assessed using the generalized Labelled Magnitude Scale.

Results: Mean daily energy intake was reduced by 27% with GOP but no significant changes in food preferences were observed, whereas a reduction in fat and increase in protein intake were seen post-RYGB. There was no change in corrected hit rates or detection thresholds for sucrose detection following GOP infusion. Additionally, GOP did not alter the intensity or consummatory reward value of sweet taste. A

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significant reduction in restraint eating, comparable to the RYGB group was observed with GOP.

Conclusion: The elevation in plasma GOP concentrations after RYGB is unlikely to mediate changes in food preferences and sweet taste function after surgery but may promote restraint eating.

KEYWORDS
antiobesity drug, bariatric surgery, GLP-1, obesity therapy, randomized trial, weight control

1 | INTRODUCTION

Roux-en-Y gastric bypass (RYGB) leads to durable weight loss up to 20 years, with substantial improvements in the metabolic state.[1] Among the proposed mechanisms for this are a switch in food preferences and eating behaviours.[2,3] After undergoing RYGB, it is well established that patients tend to eat less, have smaller meals, feel less hungry and reach satiety earlier.[4-6] Others have shown that patients consume less sugary and fatty food, with a shift towards healthier food options.[4,7-10] Patients become less preoccupied with food, do not crave or enjoy palatable food as much and work less hard for it.[3,11-15] A proposed mechanism for these observations is thought to involve changes in the sensory and hedonic domains of sweet taste, which include enhanced detection, higher intensity but reduced reward appeal following RYGB.[2] Additionally, emotional eating (eating in response to emotions), restraint eating (consciously restricting eating) and external eating (eating in response to external cues), assessed by validated questionnaires, have been shown to improve after surgery,[16-18] while disordered eating has been associated with suboptimal weight loss outcomes.[19]

Beneficial shifts in taste and eating behaviour have been reported as early as 1 to 2 months after RYGB and observed up to 11 years in longitudinal studies.[20] However, the contributing factors to these favourable changes in taste and eating behaviour after surgery remain elusive. Postprandial elevations in the gut hormones glucagon-like peptide-1 (GLP-1), oxyntomodulin (OXM) and peptide YY (PYY) have been implicated as possible drivers.[20,21] The postprandial secretion of these hormones increases several-fold early on post-surgery and high concentrations are maintained for years.[22,23] Single or combined infusions of GLP-1, OXM and PYY in humans enhance satiety, reduce food intake, and decrease activation in brain reward areas.[24-27] Additionally, GLP-1 receptors are located in the brain and on the taste buds.[28,29] It is therefore conceivable that gut hormones may be bridging factors between the sensory taste pathway and central reward pathway, ultimately mediating behavioural adaptation to food consumption post-RYGB.

We hypothesized that the elevation in the postprandial plasma concentrations of GLP-1, OXM, and PYY contributes to the beneficial changes in food preferences, sweet taste function and eating behaviour after RYGB. We replicated the postprandial concentrations of GLP-1, OXM and PYY in participants with obesity by administrating a chronic subcutaneous infusion of all three (GOP) for 4 weeks. We compared food preferences, sweet taste function, and eating behaviour using validated methods, relative to a control group, matched for age, body mass index and glycaemic control in a substudy.

2 | METHODS

2.1 | Study design and participants

This was a secondary study using data from a prospectively designed, single-blind study in which participants were randomized either to GOP or saline 0.9% infusions (ClinicalTrials.gov NCT01945840). A detailed description of the study protocol has been published elsewhere.[30] In summary, participants with obesity and prediabetes/type 2 diabetes were fitted with a subcutaneous infusion pump and combined GOP, at a dose of 4 pmol/kg/min GLP-1, 4 pmol/kg/min OXM and 0.4 pmol/kg/min PYY, or 0.9% saline was delivered. The GOP infusion doses were designed to achieve circulating concentrations of GLP-1, OXM and PYY similar to their peak postprandial concentrations, as measured 1 month after RYGB. Participants wore the pump in free-living conditions for a minimum of 12 hours during the day for 4 weeks. We included a matched RYGB group who represented the "reference" group from whom peak postprandial concentrations of GLP-1, OXM and PYY were derived at 1 month after surgery.

2.2 | Outcomes

Our study outcomes were changes in (a) food intake and preferences in the GOP, saline and RYGB groups, (b) measures of sweet taste detection (corrected hit rates and EC50) in the GOP versus saline group, (c) intensity of sweet taste in the GOP versus saline group, (d) consummatory reward value of sweet taste in the GOP versus saline group, and (e) eating behaviour in all groups.

2.3 | Food diary

Participants were instructed to complete a detailed 4-day food diary at baseline and at 4 weeks after the infusions or 1 month after RYGB. These data were analysed using Dietplan7 (Forestfield Software, UK) to derive the macronutrient composition of consumed food and mean

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24-hour energy intake (EI; kcal/d). Standardized dietetic advice on healthy eating and exercise was given to participants on GOP and saline infusions by a qualified dietician.

2.4 | Taste tests

The taste tests were performed at baseline and at week 4 of the infusions. All tests were performed in the morning after a 12-hour fast. The test was designed to assess distinct components of the sensory and hedonic domains of sweet taste function: (a) detection, (b) intensity and (c) consummatory reward value.

2.4.1 | Assessment of sweet taste detection

Sweet taste detection was measured using the method of constant stimuli. Seven different sweet solutions were prepared at room temperature using still water (Sainsbury's Caledonian still water, UK) and sucrose (Sigma-Aldrich, Dorset, UK) on the test day. These corresponded to a sucrose concentration of 2.1, 6.25, 12.5, 25, 50, 100 and 300 mM, respectively. Each solution was decanted into polyethylene cups at a volume of 15 mL. The cups were presented randomly to the participants across eight blocks, with each block consisting of seven sucrose and seven water solutions. Each concentration was represented once during each block. Participants were instructed to hold the solution in their mouth for 5 seconds and to swirl it around before splitting it out without swallowing. They were then asked whether the tested solution was "water" or "sugar" and their responses recorded. In between cups, they rinsed their mouths with the same water for 10 seconds.

2.4.2 | Data analysis for sweet taste detection

A "hit" was recorded every time the participant correctly identified the presence of sweetener in the solution. A "false alarm" was recorded for every incorrect response. The hit rate for each sucrose concentration was adjusted to account for false alarms to produce a corrected hit rate using the following equation:

$$\textit{Corrected hit rate} = \frac{P(hit) - P(FA)}{1.0 - P(FA)},$$

where $P(hit)$ represents the proportion of solutions of a given concentration that were correctly identified, and $P(FA)$ represents the proportion of solutions that were false alarms. This means that if the uncorrected hit rate is the same as the false alarm rate, the corrected hit rate would be zero.

Concentration response curves were produced to represent corrected hit rate values for each participant for each test (at baseline and 4 weeks on the infusion) in order to provide a group of individual psychometric functions using the following equation:

$$f(x) = \frac{a}{1 + 10^{((\log_{10}(x) - C) * b)}},$$

where $\log_{10}(x)$ represents $\log_{10}$ concentration, a represents the upper asymptote of performance (the maximum is 1), b represents slope, and c represents the $\log_{10}$ concentration at ½ maximum performance (EC50). The c parameter represents the threshold value as it is the inflexion point of the psychometric function, therefore, optimally represents horizontal shifts in sensitivity. The experiment only compared the c values of each of the participants' curves whose fit accounted for at least 85% of the variance, and the c values were calculated using GraphPad Prism 9.

The variables used to assess sweet taste detection were corrected hit rates, which reflected correct identification of solution as "sugar," and EC50 values, corresponding to the detection threshold.

2.4.3 | Assessment of the intensity of sweet taste

Five ascending sucrose concentrations (0, 50, 100, 200 and 400 mM) were presented to the participant across three blocks, using the same preparation protocol as described above. Each block consisted of five sucrose cups, randomly administered. The participants were instructed to rate the intensity of the solution, while holding it in their mouth, compared with the most intense taste they had ever experienced. They plotted their responses on a vertical visual analogue scale (intensity generalized Labelled Magnitude Scale [gLMS]). This ranged from zero to 200 mm (strongest taste of any kind).

2.4.4 | Assessment of the consummatory reward value of sweet taste

Assessment of the consummatory reward value ot sweet taste followed the same preparation and technique as described above and was therefore carried out at the same time. Participants were asked to rate the pleasantness of the solution tested, using a "just-about-right" (JAR) scale and a hedonic gLMS scale. The JAR scale refers to the ideal sweetness the participant would like in a sweet drink. This is a vertical visual analogue scale ranging from −100 to +100 mm, with the midpoint (zero) representing the ideal point. The hedonic gLMS is a vertical visual analogue scale which reflects how much the participant enjoys the taste of sweet solution in relation to the best taste they have ever experienced. The scale ranged from −100 to +100 mm with its midpoint (zero) representing neutral.

2.5 | Questionnaires

The following validated questionnaires of eating behaviour were completed by the GOP, saline and RYGB groups at baseline and at 4 weeks: the Dutch Eating Behaviour Questionnaire (DEBQ), which assessed restrained, emotional and external eating[31]; the Three Factor Eating Questionnaire (TFEQ), which was used to investigate eating behaviour from three dimensions: restraint, disinhibition and hunger[32]; and the Power of Food Scale (PFS), which assessed the hedonic drive to eat palatable food, independent of food consumption.[33]

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2.6 | Statistical analysis

This was a substudy analysis of prespecified secondary endpoints from a previously published randomized controlled trial, which was originally powered to detect clinically significant changes in weight with GOP infusion.[30] However, based on previous work in our department using the same methodology to investigate changes in sweet taste variables in patients undergoing RYGB at the same bariatric centre, and assuming a similar effect size with GOP, we estimated that a minimum of 10 subjects in each infusion group will give a power of 80% with an α value of 0.05.

Normality was assessed using Q-Q plots against idealized normal distributions and the Shapiro-Wilk normality test. All data are expressed as mean ± standard error of the mean, unless specified otherwise. Changes in dietary intake and questionnaire scores were compared within groups using a paired *t*-test. Two-way analysis of variance (ANOVA) with a Bonferroni post hoc test was used to compare changes in corrected hit rates and EC50s within and between the GOP and saline groups. Scaled responses from the gLMS were measured with a ruler and averaged. The effects of GOP infusion on gLMS ratings relative to saline were analysed using two-way ANOVA with a Bonferroni post hoc test. GraphPad Prism 9 (GraphPad Software) was used for analysis.

3 | RESULTS

A total of 32 participants were randomized to receive either GOP or saline infusions. Eight were excluded (four from the GOP and four from the saline group) due to technical pump issues and inability to attend study visits. Data were therefore available for a total of 15 participants in the GOP group and nine in the saline group. Food diary and eating behaviour data were also collected from 15 patients who underwent RYGB. The baseline characteristics are described in Table 1 and showed that the GOP group was well matched to the saline and RYGB groups.

3.1 | Tripeptide GOP reduces EI but does not affect food preferences

There was a significant reduction in 24-hour mean EI, as assessed by food diaries in the GOP and RYGB groups only. Both led to statistically comparable reductions in EI (−925.2 ± 153.4 vs. −683.8 ± 177 kcal/24-h; $P = 0.3$, unpaired *t*-test); however, the magnitude of EI reduction varied and was 47%, 27.3% and 15.4% across the RYGB, GOP and saline groups, respectively. Post-surgery,

TABLE 1 Characteristics of participants (mean ± SD, one-way ANOVA with Bonferroni post hoc correction for multiple comparisons, chi-squared test for non-categorical data)

	GOP n = 15	Saline n = 9	RYGB n = 15	*P* value
Sex, female:male	6:9	4:5	13:2	0.02
Age at baseline, years	55.9 ± 8.5	52.6 ± 9.0	47.1 ± 13.4	0.1
Baseline weight, kg	112.6 ± 26.7	123.3 ± 25.9	114.5 ± 24.1	0.6
Baseline BMI, kg/m^2	38.4 ± 6.9	39.3 ± 6.1	42.2 ± 5.5	0.2
Baseline HbA1c, mmol/mol	57.3 ± 15.0	49.9 ± 7.1	59.8 ± 14.2	0.2
Post-intervention weight loss, kg	4.4 ± 1.7	2.5 ± 2.6	21.3 ± 6.6	<0.0001
Post-intervention weight loss, %	4.0 ± 1.4	2.0 ± 2.0	18.4 ± 3.4	<0.0001
Post-intervention HbA1c, mmol/mol	51.9 ± 14.0	45.4 ± 4.0	40.9 ± 6.0	0.01

Abbreviations: BMI, body mass index; GOP, glucagon-like peptide-1, oxyntomodulin and peptide YY combined; HbA1c, glycated haemoglobin; RYGB, Roux-en-Y gastric bypass.

TABLE 2 Changes in mean 24-hour energy intake with macronutrient composition (paired *t*-test applied)

	RYGB		GOP		Saline		*P* values		
	Pre	Post	Pre	Post	Pre	Post	ΔRYGB	ΔGOP	ΔSaline
Mean 24-h food intake	1913 ± 157.7	987.6 ± 111.4	2021 ± 163.2	1338 ± 97.0	2084 ± 218.4	1734 ± 193.8	<.0001	.0017	.07
Δ mean 24-h food intake, kcal		−925.2 ± 153.4		−683.8 ± 177.0		−349.4 ± 164.8			
Δ mean 24-h food intake, %		47 ± 6.1		27.3 ± 8.1		15.4 ± 6.4			
Carbohydrate, %	44.8 ± 2.0	44.9 ± 2.6	41.9 ± 2.1	37.7 ± 1.9	37.8 ± 2.8	34.8 ± 3.0	.9	.1	.4
Fat, %	38.2 ± 2.2	34.4 ± 2.6	37.3 ± 1.4	38.6 ± 1.7	41.0 ± 2.3	42.6 ± 2.8	.04	.5	.6
Protein, %	16.4 ± 0.9	20.7 ± 1.4	18.1 ± 0.8	20.4 ± 1.1	18 ± 0.9	19.6 ± 0.8	.01	.1	.2

Abbreviations: GOP, glucagon-like peptide-1, oxyntomodulin and peptide YY combined; RYGB, Roux-en-Y gastric bypass.

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TABLE 3 Two-way ANOVA for within-group comparison of corrected hit rates as a function of concentration and time

	Concentration	Time (baseline vs. 4 weeks)	Concentration × time
GOP	F (6, 196) = 192.6	F (1, 196) = 0.0001	F (6, 196) = 0.69
	P = <0.0001	P = 0.99	P = 0.66
Saline	F (6, 56) = 114.7	F (1, 56) = 0.17	F (6, 56) = 0.97
	P = <0.0001	P = 0.68	P = 0.45

Abbreviation: GOP, glucagon-like peptide-1, oxyntomodulin and peptide YY combined.

TABLE 4 Two-way ANOVA for between-group comparison of corrected hit rates as a function of concentration and intervention

	Concentration	Intervention (GOP vs. saline)	Concentration × intervention
Baseline	F (6, 154) = 122.3	F (1, 154) = 1.12	F (6, 154) = 1.13
	P ≤0.0001	P = 0.29	P = 0.35
4 weeks	F (6, 154) = 176.7	F (1, 154) = 0.68	F (6, 154) = 0.39
	P < 0.0001	P = 0.41	P = 0.89

participants demonstrated a significant reduction in fat and an increase in protein intake by approximately 4%, while carbohydrate consumption was nonsignificantly decreased by approximately 3% to 4% in the GOP and saline groups (Table 2).

3.2 | Tripeptide GOP does not affect sweet taste detection

The two-way ANOVA for within-group comparisons of corrected hit rates as a function of concentration of sucrose solution and time (baseline vs. 4 weeks) is shown in Table 3. There was a significant main effect of concentration only across both infusion groups but the time × concentration interaction was not significant. This suggests that 4 weeks of GOP or saline infusion did not alter corrected hit rate results for sucrose detection compared with their respective baseline.

Table 4 provides the between-group comparison of corrected hit rates as a function of concentration of sucrose and intervention (GOP vs. saline). There was a significant main effect of concentration both at baseline and after 4 weeks of the infusions, but the concentration × intervention interaction was not significant. This suggests that both groups had comparable corrected hit rates for sucrose detection at baseline and post-intervention.

Concentration-response curves demonstrating the mean corrected hit rates for sucrose detection at baseline and after 4 weeks of both infusions are shown in Figure 1. The derived mean EC50 values at baseline were 11.3 ± 1.3 mM and 10.1 ± 2.1 mM for the GOP and saline groups, respectively, and 11.2 ± 1.3 mM (GOP) and 10.0 ± 1.2 mM (saline) post-infusions. There was no significant difference in EC50s as a function of time (baseline vs. 4 weeks, F [1, 22] = 0.004; P = 0.9), intervention (GOP vs. saline, F [1, 22] = 0.50; P = 0.5), or time × intervention (F [1, 22] = 1.6 e-005; P = 1.0).

In summary, participants did not demonstrate any enhancement in sweet taste detection based on corrected hit rates and detection thresholds with GOP or saline.

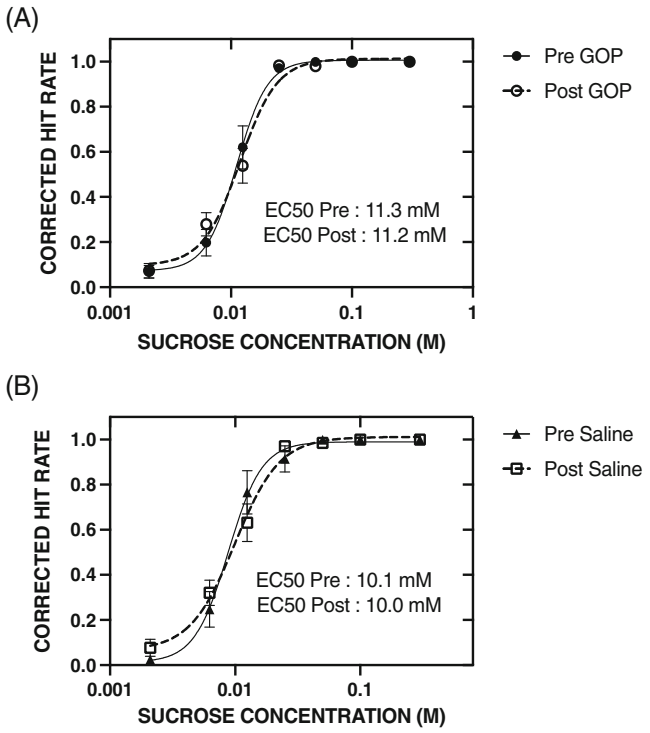


FIGURE 1 (A) Mean corrected hit rates (±SEM) at baseline (filled circles) and following 4 weeks of glucagon-like peptide-1, oxyntomodulin and peptide YY combined (GOP; open circles), plotted against sucrose concentration. (B) Mean corrected hit rates (±SEM) at baseline (filled triangles) and following 4 weeks of saline (open squares) plotted against sucrose concentration. EC50 represents the concentration at which the corrected hit rates reaches 50% of the maximum asymptote

3.3 | Tripeptide GOP does not alter intensity or consummatory reward value of sweet taste

There were no significant within-group differences in intensity of sweet taste ratings, JAR scale scores or hedonic gLMS scores for the

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TABLE 5 Mean changes in eating behaviour scores as assessed by the Dutch Eating Behaviour Questionnaire, the Power of Food Scale and the Three Factor Eating Questionnaire (paired *t*-test applied)

	RYGB		GOP		Saline		*P* values		
	Pre	Post	Pre	Post	Pre	Post	ΔRYGB	ΔGOP	ΔSaline
DEBQ - restraint	2.7 ± 0.2	3.3 ± 0.2	2.9 ± 0.2	3.3 ± 0.2	2.8 ± 0.3	3.0 ± 0.1	.008	.04	.3
DEBQ - emotional	2.7 ± 0.3	2.1 ± 0.2	2.8 ± 0.3	2.5 ± 0.3	2.6 ± 0.3	2.4 ± 0.3	.05	.5	.2
DEBQ - external	3.2 ± 0.2	2.3 ± 0.2	3.2 ± 0.1	2.9 ± 0.1	3.3 ± 0.2	3.1 ± 0.1	.0004	.06	.2
PFS	3.2 ± 0.3	2.2 ± 0.3	2.6 ± 0.2	2.3 ± 0.2	2.4 ± 0.3	2.5 ± 0.2	.009	.1	.9
TFEQ - restraint	9.1 ± 1.2	7.0 ± 1.5	9.9 ± 1.1	10.6 ± 1.3	9.4 ± 1.6	8.9 ± 1.5	.3	.4	.6
TFEQ - disinhibition	9.1 ± 0.7	6.0 ± 0.7	6.9 ± 0.9	7.3 ± 0.8	5.2 ± 1.2	6.9 ± 0.9	.002	.5	.1
TFEQ - hunger	6.7 ± 0.8	6.8 ± 0.7	6.3 ± 0.5	6.8 ± 0.4	5.9 ± 0.6	6.0 ± 0.5	.9	.5	.9

Abbreviations: DEBQ, Dutch Eating Behaviour Questionnaire; GOP, glucagon-like peptide-1, oxyntomodulin and peptide YY combined; PFS, Power of Food Scale; RYGB, Roux-en-Y gastric bypass; TFEQ, Three Factor Eating Questionnaire.

GOP or saline groups when analysed as a function of time × concentration (Data S1, Figure S1). In summary, GOP and saline participants did not experience a change in the intensity or consummatory reward value of sweet taste following the infusions.

3.4 | Tripeptide GOP promotes restraint eating

After RYGB, we observed a significant increase in restrained eating but a decrease in emotional and external eating, as measured by the DEBQ. Similar trends were also observed after 4 weeks of GOP, but only the increase in restrained eating reached statistical significance and was comparable to the RYGB group. Both the RYGB and GOP groups also displayed a reduction in PFS scores, although this was statistically significant only after surgery. The TFEQ scores demonstrated a significant reduction in disinhibition in the RYGB group only. By contrast, no significant change in any aspects of eating was found after saline infusion. A detailed summary of these changes is shown in Table 5. In summary, GOP participants seemed to experience an increase in dietary behavioural restraint similar to those who had undergone RYGB.

4 | DISCUSSION

This is the first study to directly assess the effects of a tripeptide infusion of GLP-1, OXM and PYY on food preferences in volunteers with obesity and prediabetes/diabetes and to further explore related changes in sweet taste function as potential mechanisms for shaping food choices. We also investigated the contribution of gut hormones to the healthier eating behavioural patterns reported post-RYGB. We found that elevated circulating concentrations of the gut hormones GLP-1, OXM and PYY, as observed early post-RYGB, did not alter food preferences or sweet taste function but increased restrained eating.

Infusion of GOP led to a slightly smaller but statistically comparable reduction in EI by approximately one-third relative to RYGB. However, changes in the macronutrient composition differed between the two interventions, with only the RYGB group displaying significant changes in their fat and protein intake post-surgery. Differences among the groups may be attributable to the contrasting dietary advice given to the surgical and non-surgical groups and possibly to an aversive response to fatty food post-RYGB. Reported changes in macronutrient composition post-RYGB are varied,[7,34,35] with emerging patterns suggestive of a lower intake of sweet and fatty food.[8,9] Studies using self-reported and subjective methods which fundamentally rely on accurate reporting from participants often demonstrate changes in taste and preference for low-calorie dense food, but these findings are not consistently replicated when direct measures of eating behaviour in supervised settings are used. Targeting direct eating behaviour, Nielsen et al and Livingstone et al demonstrated that food preferences do not consistently change post-RYGB in their participants, but in those where they do, it may result in additional weight loss.[36-38] It is therefore conceivable that sweet taste function may also change in some but not all patients post-RYGB, which may potentially drive the shifts away from palatable food and aid weight loss in a select few.

There are limited data on the effects of gut hormones on the gustatory pathway. GLP-1 knock-out mice showed a significant reduction in sweet taste responses in behavioural tests,[28] and peripheral administration of PYY in mice induced a conditioned taste aversion, which arguably contributes to its anorectic effects.[39] Contrary to our findings, in a study of 18 overweight individuals with type 2 diabetes, 3-month treatment with liraglutide, a GLP-1 analogue, led to improved detection thresholds to sweet taste. However, an important limitation of this study was the lack of a control group.[40] Other human studies have shown an increase in sweet taste detection acuity post-RYGB[21,41,42] using methodologies such as taste strips, or the constant stimuli or staircase methods, while some groups have shown no change in either the detection or perceived intensity of sweet taste.[16,43,44] The results of these studies should therefore be interpreted with caution. Time of testing after surgery, which spanned from 2 weeks to 1 year postoperatively, sex differences, the composition of diet at time of testing and the lack of a control group are all important considerations.

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Reported changes in the consummatory reward value of sweet taste post-RYGB are also conflicting. Pepino et al showed that participants who had undergone RYGB, but not those who had received gastric banding, experienced a switch in the palatability of sweetness from pleasant to unpleasant using the gLMS at 4 to 6 months,[16] whereas Bueter et al found no change in their cohort using similar methods. Similar to our study, their participants were tested earlier, at 1 to 2 months post-surgery.[21] Using number of licks to sucrose to assess consummatory response in rodents, Mathes et al observed no change after either RYGB or after GLP-1 receptor blockade,[45] whereas, in a study by Shin et al, rats showed a greater liking for lower compared to higher concentrations of sucrose solutions post-RYGB.[46]

A possible alternative explanation for the lack of an effect on food preferences and sweet taste in our cohort is that mechanisms other than gut hormones are involved post-RYGB. The anatomical re-routing of nutrients may be important, which was not replicated in our GOP group. However, it is worth noting that when the proximal small intestine was bypassed using a duodenal-jejunal liner (EndoBarrier), changes in sweet taste function and food preferences were not observed.[47] The extent of weight loss, in particular loss of fat mass and a reduction in leptin concentrations, could also play a role. Injecting leptin in lean mice diminished their peripheral taste nerve response to sweet stimuli, while mice with defective leptin receptors displayed an augmented response.[48] Fat mass loss differed among our cohorts, being 11.6% after RYGB, 5.8% after GOP and 2.4% after saline at 4 weeks. It has also been suggested that the perceived changes in taste by RYGB subjects may be independent of peripheral taste function but encoded by the rewarding value of food by the brain or alternatively may be shaped by post-ingestive symptoms to sugary and fatty food, such as those consistent with early and late dumping.[49,50]

Changes in dietary composition and diabetes status, have also been associated with alteration in sweet taste.[51] It should be highlighted that most studies investigating changes in sweet taste function post-RYGB recruited participants without diabetes, whereas we studied a unique cohort with prediabetes/diabetes.

Consistent with the literature, we found that post-RYGB participants demonstrated an overall healthier eating behaviour pattern, favouring long-term weight loss.[43,52,53] They were able to exercise more restraint, were less affected by emotional and external stimuli with regards to food intake, had a lower drive for palatable food and a reduction in uncontrolled eating (disinhibition). Our GOP cohort also experienced a similar increase in dietary restraint and a trend towards less external eating. There are limited data on the action of gut hormones on dietary restraint, but a central mechanism is plausible. In a study by Del Parigi et al, dietary restraint resulting in successful weight loss in obese subjects was associated with greater activation of the dorsal lateral pre-frontal cortex (DLPFC; brain areas involved in behavioural control) and lesser activation in the orbitofrontal cortex (reward brain area), compared with non-dieters, in a postprandial positron emission tomography study.[54] Both GLP-1 and PYY have been shown to reduce activation of brain reward areas and GLP-1 has been associated with increased regional cerebral blood flow within the DLPFC.[55] However, in clinical studies involving GLP-1 analogues such as liraglutide, a nonsignificant increase[56] or no change[40] in restraint eating scores were observed in participants with obesity at 1 year and 3 months, respectively.

We expected to but did not find a reduction in hedonic hunger as measured by the PFS following GOP. Studies using functional magnetic resonance imaging have highlighted a potential role for gut hormones in mediating the reward value of food. Co-infusion of PYY and GLP-1 led to a reduced activation of reward brain areas in healthy subjects compared with saline, mimicking changes of the fed state, whereas using a somatostatin analogue to block the action of gut hormones in subjects post-RYGB led to an increase in brain activation.[26,57] Furthermore, semaglutide, a GLP-1 analogue, was found to improve control of eating, to lower food pleasantness and to reduce liking for high-fat food in subjects with obesity.[58] However, a crucial difference is that these studies administered gut hormones to achieve supra-physiological circulating concentrations, whereas we targeted postprandial GOP concentrations as observed post-RYGB.

Taken together, our findings suggest that the gut hormones GLP-1, OXM and PYY, given to achieve comparable postprandial circulating concentrations as observed post-RYGB, do not alter food preferences or the sensory and hedonic domains of sweet taste. As such, they are unlikely to mediate the shifts away from sweet palatable food as reported post-RYGB. GOP potentially contributes to the reduction in EI and weight loss post-surgery by promoting dietary restraint and dampening external stimuli on food consumption.

Study limitations were its relatively short duration, and as a substudy, it was not specifically designed to test the effect of GOP on the prespecified secondary outcomes reported here. Ultimately, longer-term studies using direct and objective testing methods to explore food preferences and sweet taste modulation as primary outcomes are needed to understand the mechanisms engendering the changes in food choices and eating behaviour after RYGB.

AUTHORS CONTRIBUTIONS

Design: Alexander D. Miras, Stephen R. Bloom, Tricia M. Tan; Study conduct/Data collection: Preeshila Behary, Haya Alessimii, George Tharakan, Kleopatra Alexiadou, Sanjay Purkayasha, Krishna Moorthy, Ahmed R. Ahmed; Analysis: Preeshila Behary, Haya Alessimii, Madhawi M. Aldhwayan, Tricia M. Tan; Writing manuscript: Preeshila Behary with input from Haya Alessimii, Alexander D. Miras, Madhawi M. Aldhwayan, Tricia M. Tan. All authors reviewed and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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