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The role of vagal activation in postprandial glucose metabolism after gastric bypass in individuals with and without hypoglycemia

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Abstract

Patients with gastric bypass surgery (GB) have enhanced postprandial hyperinsulinemia and incretin effect. Here we sought to determine the effect of vagal activation, a neural component of the enteroinsular axis, on postprandial glucose metabolism in patients with and without hypoglycemia after GB.

Seven subjects with documented post-GB hypoglycemia (HGB), 7 GB subjects without hypoglycemia (AGB), and 10 weight-matched non-surgical controls with normal glucose tolerance (CN) were recruited. Blood glucose, and islet hormone and incretin secretion were compared during mixed meal tolerance tests (MTT) with and without prior sham-feeding on two separate days.

Sham feeding preceding the MTT caused a more rapid increase in prandial blood glucose but lowered overall glycemia in all 3 groups ($p < 0.05$). Sham feeding had a comparable effect to increase early ($p < 0.05$), but not overall, meal-induced insulin secretion in 3 groups. Prandial glucagon concentrations were significantly greater in GB subjects and sham feeding accentuated this response ($p < 0.05$).

Conclusion: The effect of vagal activation on prandial glucose and islet-cell function is preserved in subjects after GB, both with and without hypoglycemia.

INTRODUCTION

The use of bariatric surgery has increased in clinical practice over the past two decades because it is the most effective intervention for weight loss, and has profound immediate

effects on glucose metabolism¹. Procedures such as gastric bypass (GB) induce diabetes remission in up to 50% of affected patients^{2,3}. Surgical rearrangement of the gastrointestinal (GI) tract with GB causes rapid passage of nutrients into the small bowel, increased rates of nutrient appearance into the circulation⁴, and augmented postprandial glycemic peaks⁴. However, people with GB have enhanced insulin secretion that contributes to rapid and efficient glucose clearance^{4–6}. It is likely that improved β -cell function contributes to the rapid improvement in diabetes after surgery. However, in a subset of patients this effect is exaggerated causing a syndrome of hyperinsulinemic postprandial hypoglycemia^{5,7}.

Augmentation of prandial insulin secretion after GB has been attributed to greater glycemic stimulus and also to the effects of insulinotropic factors released from the gut⁶. There is evidence for increased stimulation by the incretin glucagon-like peptide 1 (GLP-1) after GB⁸, but it is not clear that this explains the entirety of enhanced β -cell secretion after surgery or whether other regulatory factors account for the pathologic insulin responses in subjects with post-bariatric hypoglycemia (PBH).

It has long been known that the central nervous system (CNS) regulates islet hormone secretion. An early demonstration of neural regulation of insulin release was in rats fed sham meals, or entrained to stimuli related to eating⁹. This response, termed cephalic insulin release, has also been demonstrated in humans^{10,11}, and can improve glucose tolerance^{10,12}. Both cephalic¹¹ and prandial¹⁰ insulin secretion is mediated in great part by parasympathetic stimuli carried in the vagus nerve^{9,12–14}. It is clear that GB has substantial effects on brain centers controlling feeding behavior¹⁵. Thus, it is plausible that the CNS also affects islet hormone release after surgery. In this study we tested the hypothesis that cephalic insulin secretion is retained after GB, but differs between post-surgical patients with and without hypoglycemia (see Supplementary Methods).

RESULTS

Subject characteristics (Supplementary Table)

The HGB and AGB groups had similar values for age, preoperative BMI, total weight loss, and time since GB. Control subjects had similar BMI and A1C values as the surgical groups, although they were younger. Measured waist circumference, fat mass, and lean mass were not significantly different among the three groups.

Glycemic response during meal studies (Fig. 1A, Table 1)

Fasting glucose levels were similar among the three groups. After meal ingestion the rise in blood glucose diverged significantly between the GB subjects and the non-operated controls as early as 8 min postprandial, leading to larger $AUC_{\text{Glucose}(0,30\text{min})}$ in the surgical groups; this is a well described characteristic of GB. Despite altered glucose responses in the GB groups, $AUC_{\text{Glucose}(0,180\text{min})}$ was not different between the AGB and CN groups. During the MTT studies all HGB subjects became symptomatic coincident with low blood glucose levels within 60–120 minutes from meal ingestion. As a result, their overall glucose response ($AUC_{\text{Glucose}(0,180\text{min})}$) was significantly less than the other two groups, neither of which had any subject develop symptomatic or biochemical (< 2.8 mM) hypoglycemia.

There was no significant correlation between nadir glucose values and baseline characteristics such as age, BMI, and either time lapsed, or weight loss, since surgery.

Sham feeding altered the postprandial glucose profiles in all three groups by increasing the rise of glucose shortly after meal consumption and reducing overall prandial glycemia as reflected in lower glucose nadir and lower $AUC_{\text{Glucose}(0,180\text{min})}$.

Postprandial islet-cell secretion with and without sham-feeding (Fig. 1B&C, Table 1)

Fasting insulin was significantly higher in the controls compared to the surgical groups. However, the post-surgical subjects had significantly greater early β -cell responses to the MTT than CN individuals. The divergence of insulin secretion was evident as early as 6 min from meal ingestion between the GB and CN groups, but $AUC_{\text{Insulin}(0,180\text{min})}$ and $AUC_{\text{ISR}(0,180\text{min})}$ was similar among the three groups. Sham feeding enhanced the early β -cell secretory responses in all groups, an effect most apparent in the AGB and CN subjects. Sham feeding also caused a significant decrease in glycemia after the MTT, $AUC_{\text{Glucose}(0,180\text{min})}$ in all groups.

Fasting levels of plasma glucagon were similar among the three groups, and similar to the insulin responses prandial glucagon secretion was greater in the GB than CN subjects; there were no differences between AGB and HGB cohorts despite hypoglycemia in the latter group during the MTT. Fasting values of PP did not differ among the three groups but early meal-induced PP secretion was greater in the AGB subjects compared to both HGB and CN subjects (Supplementary Fig.1). The addition of sham feeding to the MTT enhanced the early glucagon and PP responses in all three groups.

Insulin sensitivity and clearance, and disposition index (Table 1):

There was a trend toward higher MTT-derived insulin sensitivity (OGIS) in the GB subjects compared to non-surgical subjects. The values of oral disposition index during the MTT studies were notably larger in the GB subjects compared to controls, but did not differ between the HGB and AGB groups. Fasting insulin clearance was also significantly greater in the GB compared to CN subjects, whereas postprandial insulin clearance did not differ among the groups. Sham feeding had no influence on OGIS or postprandial insulin clearance, although oral disposition indices were augmented in all three groups by sham-feeding.

Meal-induced incretin response (Supplementary Fig.2):

Circulating levels of GLP-1 were similar among the three groups at baseline but $AUC_{\text{GLP-1}(0,180\text{min})}$ was significantly larger in surgical patients compared to the CN, with higher levels in the HGB compared to the AGB subjects ($p < 0.0001$). Fasting levels of GIP were different among the three groups with the highest values found in the AGB individuals. Compared to the CN, surgical patients had a slightly earlier post-meal GIP response, but $AUC_{\text{GIP-1}(0,150\text{min})}$ was not different among GB or non-surgical patients. Sham feeding did not affect postprandial GLP-1 responses, but meal-induced GIP secretion was increased significantly in all groups during Shm+MTT, without any change in pattern of GIP response.

DISCUSSION

Neural factors contribute to postprandial glucose metabolism, and this has been best established for parasympathetic control of islet hormones. To our knowledge this system has not been previously investigated in the context of GB in humans. Here we demonstrate that vagal activation by food-related oral stimulation is retained in subjects after GB surgery, and that the effect is consistent and comparable to a matched CN group without surgery. Sham feeding increased glycemic, insulin, glucagon and GIP responses to a test meal in GB subjects. However, responses to sham feeding-induced did not distinguish GB subjects with hypoglycemia from those without. These results indicate that neural control of islet function is maintained after surgery, and raise the possibility that the brain coordinates adaptations of insulin and glucagon secretion to other metabolic alterations after GB.

In this study sham feeding was used to stimulate vagal activity, an effect demonstrated in previous studies of humans before and after truncal or gastric vagotomy¹⁶. This paradigm has been validated as activating cephalic phase (ie. neural) stimulation of the islet¹¹, and can be applied before meals to assess effects on glucose tolerance¹⁰. Our findings in the CN subjects are consistent with previous reports using this protocol that showed greater early insulin secretion and improved glucose tolerance in nonsurgical subjects¹⁰.

The major finding in this study was that the cephalic insulin response was intact in GB subjects, and comparable to controls without surgery. The rise in postprandial ISR when sham feeding was used for vagal activation preceded corresponding changes in systemic glucose levels by 5–10 minutes, consistent with vagally-induced β -cell secretion independent of systemic glucose levels, and comparable to the response in CN. The effect of sham feeding to increase early insulin secretion was most evident in the AGB and CN subjects, both of whom had a nearly 40% rise due to vagal activation. The HGB subjects tended to have larger early insulin responses to meals and smaller effect of sham feeding compared to the AGB subjects. However, we did not find an interaction between group and day effects on $AUC_{ISR(0,30min)}$, indicative of a difference attributable to both variables. The lack of an effect here may be due to lack of statistical power from our limited sample size. Whether subtle differences in neutrally mediated islet function are present in, and perhaps contribute to, the postprandial hypoglycemia syndrome will require more detailed study.

In addition to the effects of sham feeding on β -cell secretion, early α - and PP-cell responses to meal ingestion were increased as a result of vagal activation. A large body of evidence supports the role of the parasympathetic nervous system as contributing to the control of glucagon secretion¹⁷. In our study meal-induced glucagon was significantly higher in GB than CN subjects, similar to what has been observed previously. Moreover, sham feeding increased early glucagon responses in the GB subjects with only minimal effects in the CN group, raising the possibility that increased neural input to α -cells after GB surgery accounts for the relative postprandial hyperglucagonemia; this would require more detailed studies of glucagon secretion and sensitivity in GB and controls subjects.

Our findings indicate an effect of vagal activation not just on islet hormone secretion but also GI function. Blood glucose was identical in each group at the beginning of the MTT

with and without sham feeding, but glycemia rose more quickly when vagal function was activated. We did not measure gastric/gastric pouch emptying and so cannot comment on whether sham feeding increased the rate of passage of nutrients into the intestine. Whether sham feeding promotes intestinal glucose uptake is also an open question. The increased GIP response after sham feeding is consistent with more rapid passage of nutrients through the intestine¹⁸, although we cannot exclude direct parasympathetic stimulation of GIP-secreting K cells in this effect. It is not clear why GLP-1, which shows enhanced secretion with more rapid appearance of glucose in the gut¹⁹, was not affected similarly.

There are several limitations of our study that are important to note. First, the number of subjects was small and this limits the statistical power of the observations. A second limitation is the absence of formal measures of nutrient and GI fluxes. This restricts our ability to comment on some of the positive effects of sham feeding, particularly those related to the early glycemic response. Finally, we have inferred vagal, parasympathetic signaling as responsible for the results of sham feeding. This has been demonstrated in the past with sophisticated physiologic testing¹⁰, and we have relied on this procedure as established based on these studies.

Altogether our results indicate that sham feeding exaggerates the insulin, glucagon and glycemic responses to meals that are characteristic of GB. This indicates that islet innervation by parasympathetic nerves carried in the vagus is intact after GB, and affects both α - and β -cells. While we did not see clear differences in sham feeding effects between AGB and HGB subjects, in this small study we cannot exclude a difference in islet neural function that contributes to the postprandial hypoglycemia syndrome. Regardless, the evidence for acute neural regulation of meal-induced insulin secretion raises the possibility that chronic effects of GB on islet function and glucose metabolism are also integrated in the CNS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(A) Blood glucose, (B) insulin, and (C) glucagon secretory response to meal ingestion preceded by a sham feeding (Shm+MTT, solid line, black bar) or not (MTT, dotted line, white bar) in the post-surgical subjects with (HGB) and without (AGB) hypoglycemia as well as non-operated controls (CN). The corresponding areas under curve values for both 0 to 30 minutes as well as the entire study (0 to 180 minutes) are shown (insets). Data are presented as mean $\pm$ SEM. * $p < 0.05$ ** $p < 0.01$ compared to CN and § $p < 0.01$ compared to HGB (group effect), φ $p < 0.05$ compared with MTT alone (sham feeding effect)

Blood glucose and islet-cell response during meal ingestion with and without preceding sham feeding among patients with hypoglycemia after gastric bypass (HGB), asymptomatic subjects with history of gastric bypass (AGB) and non-operated healthy controls (CN)

Table 1.

	MTT			Shm+MTT			P values	
	HGB	AGB	CN	HGB	AGB	CN	Day	Group
Fasting glucose (mmol/L)	4.3±0.2 **	4.5±0.2	4.7±0.1	4.4±0.1	4.5±0.1	4.7±0.1	0.527	0.200
Time to reach peak glucose (min)	32.1±2.1 *	39.3±8.9 *	66.5±10	32.9±3.4	27.1±1.8	40.5±3.9	0.009	0.014
Time to reach nadir glucose (min)	98.6±7.9 **	158.6±16.9 §	153±12.2	92.1±7.6	128.6±15.6	144±14	0.118	0.004
Nadir glucose (mM)	2.4±0.3 **	4.4±0.4 §§	5±0.2	2.1±0.2	3.9±0.3	4.9±0.1	0.007	0.000
Peak glucose (mM)	9.3±0.5 **	9.1±0.4 **	6.6±0.2	9.1±0.5	9.6±0.5	6.6±0.2	0.394	0.000
Glucose excursion (mM)	6.9±0.4 **	4.7±0.8 §	1.6±0.2	7±0.5	5.6±0.8	1.7±0.2	0.007	0.000
Fasting insulin (pmol/l)	32.3±4.8 *	50.4±13.6	101.9±22.5	35.3±4.4	49.8±11.9	101.5±17.2	0.900	0.010
Fasting ISR (pmol/min)	104.5±17.7	159.6±63.1	209.7±38.1	115.1±24.5	156±38	217.2±51.7	0.723	0.226
Time to reach peak ISR	47.1±2.1 **	47.9±9.7 **	99±11.7	49.3±2.8	41.4±4.8	64.5±8.4	0.036	0.001
Peak ISR (nmol/l)	2.1±0.3 *	1.4±0.2	1.1±0.2	2.3±0.4	1.9±0.3	1.2±0.4	0.135	0.033
Fasting GLP-1	6.0±50.8	10.4±2.8	6.8±1.0	5.7±1.0	8.6±1.2	6.2±1.1	0.234	0.711
Fasting GIP	52.7±7.9	71.8±9.4 *	37.4±6.3	65.1±11.8	71.7±6.6	41.8±6.2	0.113	0.350
Fasting Glucagon	31.0±5.4	46.4±6.2	36.8±3.8	32.0±4.5	39.7±7.9	39.4±5.0	0.795	0.578
Fasting PP (pg/ml)	61±18	100±34	164±55	80±28	202±120	157±58	0.303	0.461
AUC _{pp} (0.30min) (ng. mL ⁻¹ .min)	1.4±0.4	3.7±2.3 **§	1.2±0.3	1.8±0.6	13.3±6.0	2.9±0.8	0.040	0.130
Fasting Insulin clearance	3.4±0.5 *	3.2±0.5	2.2±0.2	3.3±0.5	3.2±0.2	2.1±0.2	0.718	0.020
Prandial insulin clearance	1.4±0.3	1.5±0.2	1.6±0.1	1.4±0.3	1.5±0.2	1.3±0.1	0.580	0.798
OGIS (mL.min ⁻¹ .m ⁻²)	424±32	445±35	392±16	403±38	415±28	393±13	0.140	0.058
Disposition Index	7862±1664 **	4951±739 *	1563±364	8782±1712	6796±1341	2775±660	0.006	0.700

Data are presented as mean ± SEM. AUC, incremental areas under the curve; ISR, insulin secretion rate; OGIS, meal-derived glucose insensitivity. Statistical effects (main effects of study day [Shm+MTT/MTT] and group status [HGB/AGB/CN], as well as their interaction [study day*group status]) are provided in the last three right-hand columns.

* p < 0.05 and
** p < 0.01

p<0.01 compared with HGB (Post-hoc Bonferroni adjustment for within group analysis when indicated)

p<0.05 and

p<0.01 compared with CN

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