Regulation of gastric emptying rate and its role in nutrient-induced GLP-1 secretion in rats after vertical sleeve gastrectomy

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glucagon-like peptide-1

THE MOST EFFECTIVE TREATMENT OPTION currently available for obese and overweight patients seeking significant and lasting weight loss is bariatric surgery. Roux-en-Y gastric bypass (RYGB), currently the most widely utilized bariatric surgery, results in ~30% excess weight loss and substantial improvements in metabolic comorbidities (5). RYGB involves a 90% reduction of stomach size and reconfiguration of the intestine whereby the pylorus, duodenum, and upper jejunum are completely excluded from nutrient exposure. Recently, the vertical sleeve gastrectomy (VSG) has gained popularity because of its simplicity and comparable efficacy with RYGB (7, 10, 18, 22, 33, 37). In VSG ~80% of the stomach is removed along the greater curvature, and there is no physical manipulation of the pylorus or intestine.

Despite the dramatic anatomic differences, RYGB and VSG cause similar weight loss, improvements in glucose regulation, and increases in nutrient-dependent secretion of gut hormones (7, 33, 37). Both surgeries also produce long-term reductions in food intake and reduced meal size (8, 41, 51). Following meal ingestion, glucose levels rise rapidly in persons with RYBG or VSG, but clearance is rapid, and overall glucose tolerance improves in both diabetic and nondiabetic individuals (3, 37). This pattern of postprandial glucose excursion is due in great part to increased entry of meal glucose from the gut following RYGB (34). Increased nutrient delivery to the intestine has also been hypothesized to be the mechanism by which glucagon-like peptide-1 (GLP-1) release is enhanced after bariatric surgery. Most studies of humans with RYGB or VSG report increased rates of gastric emptying (2, 4, 27–30, 40); for VSG this was unanticipated, since the procedure preserves the pylorus (24). There is strong evidence from human studies that GLP-1 secretion is dependent primarily on rates of glucose appearance in the intestine (38, 39).

The rate of gastric emptying is controlled by mechanical factors in the stomach that are related primarily to volume and pressure but also inhibited though endocrine and neuronal inputs from the intestinal tract tied to nutrient absorption (6, 13). This complex regulatory system governs the appearance of carbohydrates and other nutrients into circulation and to critical organs such as the liver. In this study, indices of gastric emptying rate were optimized in surgically naïve rats and then assessed in sham- and bariatric-operated animals, using imaging and biochemical techniques. These models were used to explore the neuronal and endocrine regulation of gastric emptying after VSG along with the postingestive consequences of faster gastric emptying insulin and GLP-1 secretion.

METHODS

Animals. Male Long-Evans rats were purchased from Harlan (Indianapolis, IN) and housed singly in the University of Cincinnati Laboratory Animals for Medical Science Facility at the Metabolic Diseases Institute under controlled conditions (12:12-h light-dark cycle, 50–60% humidity, 25°C). Animals had free access to standard rodent chow or high-fat diet and water unless noted. All procedures for animal use were approved by the University of Cincinnati Institutional Animal Care and Use Committee.

Surgery. Animals received bariatric surgeries using standardized surgical procedures (7, 8). Before surgery, rats were given ad libitum access to water and a high (butter)-fat diet (4.5 kcal/g, 41% fat; 0193-1849/14 Copyright © 2014 the American Physiological Society
Research Diets, New Brunswick, NJ) that was previously documented to produce significant weight gain and metabolic impairment (49). After 8 wk on a high-fat diet, fat mass was assessed using NMR (Echo MRI; Echo Medical Systems, Houston, TX) and used to assign surgical groups (RYGB, VSG, or sham) in a counterbalanced fashion. Surgeries and postoperative care were performed as described previously (7, 8).

Imaging/scintigraphy. Rats were anesthetized with isoflurane and gavaged with either 2.5 ml of a liquid nutrient solution (Ensure Plus; Abbott, Columbus, OH) containing 37 MBq (1 mCi) of 99mTc Sulfur Colloid (99mTc SC) or a mixture of Ensure (1 ml) and barium sulfate (2.5 ml, 70% wt/vol) for X-ray visualization of GI anatomy. Immediately after the gavage, animals were placed in a supine position on the imaging tray and maintained under anesthesia. For the tracer studies, a radioisotopic phosphor screen was placed between the charge-coupled device camera and the imaging tray to allow for visualization of the isotope. A 230-s radioisotopic exposure of the stomach was taken every 5 min for 1 h (Carestream MS FX PRO, Woodbridge, CT). Prior to the 1-h radioisotopic study, an X-ray (30-s exposure with no filtering) was taken for anatomic reference. The radioisotopic data were processed by converting the images to photons·s⁻¹·mm². An auto region of interest (ROI) was drawn around the Ensure-99mTc mixture in the stomach using a threshold method where the lower limit is the minimum photon intensity in the 100% gastric content image (see Fig. 1). For consistency, all images were displayed and evaluated with the same minimum photon intensity value. An autogenerated background (background nos. were within 99.6% of each other) was subtracted from each image. The change in net photon intensity over time was used as an index of gastric emptying rate. For the contrast studies, a radiographic phosphor screen was placed between the charge-coupled device camera and the imaging tray to obtain the X-ray images. A manual ROI was drawn around the stomach, visualized by the barium. Background-subtracted net X-ray intensity values were obtained from stomach ROIs for comparison evaluation between surgery rat groups (Fig. 2). Chemical tracer techniques for measuring gastric emptying. Overnight-fasted, chow-fed Long-Evans rats with no prior surgical interventions were weighed and moved to a procedure room and allowed to acclimate for 2 h. Weight-matched groups had a baseline blood sample taken from a tail vein and were given an intraperitoneal (ip) injection of atropine, a muscarinic receptor antagonist known to inhibit gastric emptying, carbachol, an acetylcholine receptor agonist known to increase gastric emptying, or saline (n = 6/group). Animals were gavaged with a mixed volume (6 ml) of D-[¹⁴C]glucose (20 μCi), acetaminophen (100 mg/kg), and D-xylose (0.5 g/kg) and sampled at 10, 20, 30, 45, and 60 min after the gavage. A similar gavage procedure was used to study RYGB (n = 5), VSG (n = 7), or sham (n = 7), but with a 3-ml volume, and toluidine blue was added to the liquid gavage mixture for postmortem measurement of transit of chyme through the intestine. For this assessment the intestine was carefully removed and stretched to full length, and the length containing dye was compared with the total length of the small intestine. For RYGB rats, the bilipancreatic limb was included in total gut length to account for reflux into this region.

Pressure and volume effects. Gastric pressure was measured in a separate group of animals 6 mo after VSG or sham surgery (n = 8/group). The pylorus and esophagus were ligated immediately after euthanasia. Three milliliters of saline was infused into the stomach, and pressure was measured using a transducer (PX26–005GV; Omega Engineering, Stamford, CT). In a group of conscious rats with VSG or sham operations (n = 4–5/group), the effect of volume on gastric emptying was studied using gavage of 0.3, 1, or 3.0 ml of a viscous mixture of 2% methylcellulose and D-[¹⁴C]glucose (14.7 μCi). The appearance of ¹⁴C in plasma between 0 and 60 min was used as an index of gastric emptying.

Neural influences on gastric emptying. Four months after surgery, atropine (1 mg/kg ip) was given to overnight-fasted sham- or VSG-operated rats (n = 5/group) 15 min prior to orally delivered 50% dextrose (2.0 ml) mixed with an acetaminophen tracer (100 mg/kg) to Fig. 1. A: representative radioisotopic/X-ray overlay images showing gastric visualization of 99mTc Sulfur Colloid/Ensure mixture in rat stomach at time 0 and 60 min following oral gavage. B: changes in net photon intensity over time were used to index the rate of gastric emptying. C: plasma levels of 3 different markers for gastric emptying. [¹⁴C]glucose, acetaminophen (acetamin), and D-xylose, after intraperitoneal (ip) saline (○), atropine (red circles), or carbachol (●). Left: [¹⁴C]glucose levels were significantly higher after ip treatment with carbachol and significantly lower after ip atropine. *P < 0.05 vs. saline (Bonferroni posttests). Middle: atropine significantly reduced acetaminophen levels compared with saline treatment; *P < 0.05. Right: plasma levels of D-xylose were unaffected by ip treatment with atropine or carbachol compared with saline treatment.
study neural influences on gastric emptying. Plasma was sampled for the appearance of tracer at 0- and 10-min time points. Effects of GLP-1 receptor activation on gastric emptying in VSG. Six months after surgery, rats with VSG (n/H11005 4) or sham (n/H11005 5) were administered saline or the GLP-1 receptor agonist exendin-4 (50 g/kg ip) 15 min prior to orally delivered 50% dextrose (2.0 ml) mixed with acetaminophen (100 mg/kg). All experiments were performed following an overnight fast, and each animal went through each condition via a counterbalance design. Blood samples were collected at 0 and 10 min. The role of endogenous GLP-1 secretion on gastric emptying after VSG was investigated in GLP-1R-knockout (n/H11005 28) and wild-type littermate control mice (n/H11005 14) 6 wk following VSG or a sham operation, as described previously (8). Mice were given an intraoral infusion of liquid diet (200 l of Ensure Plus) mixed with acetaminophen (100 mg/kg) and blood sampled at 0 and 10 min. Mice in this experiment were previously part of another study (43).

**Assays.** To measure plasma content of D-[14C]glucose, samples were deproteinized with BaOH and ZnSO4, and -counting was performed with standard scintillant. Plasma D-xylose and acetaminophen were measured by calorimetric assay, as described previously (23, 36). Insulin was measured by ELISA (Crystal Chem, Downers Grove, IL), and GLP-1 was measured using MSD mesoscale assay (Gaithersburg, MD) according to the manufacturer’s instructions.

**Statistical analysis.** The primary data analysis was conducted with mixed-model ANOVAs, using treatment and surgery as the active factors. Bonferroni’s post hoc test was performed for direct comparisons of individual groups. Two-tailed t-tests were used for comparisons of two groups. Statistical significance was set at P < 0.05 for all analyses. Data are presented as means ± SE.

**RESULTS**

**Scintigraphy and chemical tracer techniques.** In rats given a mixed liquid meal containing 99mTc SC, there was a linear decrease in the stomach contents over time. This was anatomically verified in a second experiment in the same rats with a gavage of barium plus liquid meal. Figure 1, A and B, displays a representative image from the overlay of the 99mTc images. In tests of surrogate measurements of gastric emptying in conscious rats, atropine and carbachol were given to decrease and increase gastric emptying rates, respectively. Plasma levels of n-[14C]glucose, acetaminophen, and D-xylose during these
treatments are depicted in Fig. 1C. The pharmacological inhibition of gastric emptying by atropine was observed using both $^{14}$C and acetaminophen tracers relative to saline- or carbachol-treated animals. However, plasma levels of $\alpha$-xylose were similar between the three treatment groups. These data indicate that $^{14}$C-labeled glucose and acetaminophen were better markers of gastric emptying rate, as both reflected the expected change in gastric emptying rate induced by carbachol and atropine compared with saline-treated animals.

Gastric emptying dynamics following bariatric surgery. VSG and RYGB rats lost similar amounts of weight and were significantly lighter than sham-operated controls (Fig. 2A). There was significant passage of barium into the intestine of RYBG and VSG animals within the first 5 min following gavage, whereas little contrast passed from the stomach of sham animals (Fig. 2B). When this measurement was quantified with $^{99m}$Tc SC, the liquid meal mixture was $100 \pm 0\%$ emptied from the pouch in RYGB rats and stomach in VSG animals in 5 min, whereas only $6.1 \pm 6\%$ was emptied from sham stomachs over this period (Fig. 2C). In fact, only $24 \pm 15\%$ of administered tracer mixture passed from the stomach of the control animals by 60 min after the gavage. $\alpha$-[14C]glucose and acetaminophen also appeared much more rapidly in the plasma of RYGB and VSG rats compared with the sham animals, whereas plasma concentrations of $\alpha$-xylose did not differ among groups. Faster gastric emptying rates were also associated with faster transit times. The passage of chyme labeled with toluidine blue traveled twice the distance down the GI tract in VSG (73 $\pm$ 11%) and RYGB (73 $\pm$ 5%) compared with sham animals (36 $\pm$ 11%) (Fig. 2E). Interestingly, dye was observed in the bypassed region of RYGB rats, suggesting some reflux through the jejunostomy. Despite this, the distance of the dye from the terminal ileum was similar between VSG (33 $\pm$ 13 cm) and RYGB (38 $\pm$ 7 cm) rats, implying that nutrients reached the same cell populations at a similar rate in these animals. Gastric pressure was significantly elevated after VSG (4.43 $\pm$ 0.25 mmHg) vs. sham (1.74 $\pm$ 0.13 mmHg) surgery (Fig. 2F), as expected. Because of the open system produced by RYGB, gastric pressure could not be measured in these animals.

Regulation of gastric emptying by gavage volume. The effects of different gavage volumes on gastric emptying were studied using a noncaloric infusate (Fig. 3, A–D). The range of volumes tested was based on what animals were observed to eat voluntarily following VSG (8, 11). Rates of radiolabeled glucose appearance did not differ among sham and VSG animals gavaged with 0.3- to 2.0-ml volumes of the infusate. However, when administered at a volume of 3.0 ml, gastric emptying rates were significantly greater in VSG rats compared with sham animals ($P < 0.05$).

Neural and GLP-1R-mediated influences on gastric emptying. Innervation of gastric smooth muscle by efferent nerves inhibits motility through muscarinic receptor activation. As expected, gastric emptying was delayed in sham-operated rats given the muscarinic antagonist atropine compared with saline-treated rats (Fig. 4A). However, VSG rats were unresponsive to atropine, indicating that surgery abolished much of the neural regulation on gastric emptying in these animals.

Hormones released from the distal intestine, such as GLP-1, inhibit gastric emptying, a phenomenon referred to as the ileal brake. To test this effect in animals with VSG, the GLP-1R agonist exendin-4 was administered before a gavage of glucose and acetaminophen. In sham-operated rats, exendin-4 delayed gastric emptying compared with saline pretreatment, as expected (Fig. 4B). However, exendin-4 did not affect gastric emptying in VSG animals. To assess the role of endogenous GLP-1 on gastric motility after VSG, mice with targeted deletion of the GLP-1R were studied. Consistent with the pharmacological data, the absence of GLP-1R signaling did not alter gastric emptying in mice that received VSG compared

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**Fig. 3.** A–D: gastric emptying in sham (○) and VSG (●) rats orally gavaged with different volumes (0.3–3.0 ml) of a noncaloric methylcellulose solution mixed with $^{14}$C-labeled glucose. A–D, insets: area under the curve (AUC). *$P < 0.05$ compared with sham (Bonferroni posttests).
tions of nutrients were infused directly into the duodenum of the intestine, equivalent concentrations of nutrients were infused directly into the duodenum of sham- and VSG-operated animals at identical rates. As expected, in rats given an oral nutrient gavage, plasma GLP-1 levels were significantly greater in VSG rats compared with controls (Fig. 7). Interestingly, the same increase was seen when nutrients were infused directly into the duodenum, indicating that intestinal factors contribute to increased GLP-1 secretion following surgery.

**DISCUSSION**

The mechanisms underlying the success of bariatric surgery on weight loss and obesity-related comorbidities are still not clearly understood. We have developed rodent models of RYGB and VSG and in previous studies have demonstrated that these surgeries have comparable metabolic effects that are mediated through mechanisms beyond simple gastric restriction (7, 10, 11, 41, 42, 48). A central conundrum is the similar beneficial effects of RYGB and VSG, procedures that result in very different GI anatomy. In this study, we demonstrate that both VSG and RYGB also share rapid emptying of nutrients from the stomach into the intestine as a surgical effect. This was a consistent finding regardless of the technique used to assess gastric emptying rate. Moreover, we found that animals with VSG lose their response to many of the regulatory signals that normally control gastric emptying rate. It is also notable that VSG increased nutrient-induced GLP-1 secretion independent of the rate of delivery of nutrients into the intestine. We hypothesize that the chronic exposure of high-nutrient flux into the intestine enhances intestinal nutrient-sensing and ultimately enhances the metabolic effects of the surgery.

Faster gastric emptying rates after VSG may result from the loss of receptive relaxation and the accommodation reflexes, a process whereby the stomach receives increasing volumes without concomitant increases in intragastric pressure (19). This reservoir function is specific to the proximal stomach, and removal of this region greatly increases intragastric pressure, resulting in accelerated gastric emptying (19). Therefore, it is possible that a similar process is responsible for the accelerated gastric emptying produced by VSG. Consistent with this hypothesis, patients that undergo subtotal gastrectomy to remove tumors or treat intractable peptic ulcers also display a pattern of accelerated glucose appearance and greater insulin secretion during meals (31, 35). Such patients are generally not obese, and changes in nutrient handling are regarded as an unwanted but tolerable side effect (31, 35). More recently, however, therapeutic potential for accelerated gastric emptying has been identified (28, 46). Therefore, in the present study we examined how changes in gastric emptying are potentially involved in the alleviation of metabolic derangements after bariatric surgery.

Although scintigraphy is a powerful method for assessing gastric emptying, it is a technique that may not be available to all investigators or for all experimental designs in rodent models. Therefore, we compared three different biochemical tracers as a means of indirect assessment of gastric emptying and the presentation of nutrients in plasma and with critical tracers as a means of indirect assessment of gastric emptying.

**Regulation of gastric emptying by nutrients.** To investigate the role of nutrient density on gastric emptying, rats were given different amounts of carbohydrate or fat in a fixed volume. In sham-operated rats there was inhibition of gastric emptying with increasing density of both carbohydrate and fat calories (Fig. 5, A–D). However, in animals with VSG, gastric emptying was increased and did not differ among the caloric loads. In this set of experiments, VSG rats had greater prandial insulin secretion and lower glucose excursions than sham-operated animals (Fig. 4, A).

**Intestinal nutrient sensing and GLP-1 secretion.** GLP-1 release is increased following bariatric surgery. To test the hypothesis that this response is determined by differences in the flux of nutrients into the intestine, equivalent concentrations of nutrients were infused directly into the duodenum of wild-type animals (Fig. 4C), implying that increased endogenous GLP-1 secretion after VSG has a minimal effect on gastric emptying.

**Fig. 4.** A: gastric emptying in sham and VSG rats after ip saline or atropine injections. *P < 0.05 vs. saline (Bonferroni posttests). B: gastric emptying in Sham and VSG rats treated with either vehicle or exendin-4 (Exn-4). *P < 0.05 compared with saline. C: gastric emptying in wild-type (WT) or glucagon-like peptide-1 (GLP-1) receptor-deficient (GLP-1R KO) mice that underwent VSG or a sham operation. Note that gastric emptying was increased by VSG to a similar degree in both genotypes; P > 0.05 vs. WT.
between pharmacological and surgical manipulations on gastric function. A key reason for this may be because there is gastric absorption of D-xylose in rats (45), which would tend to blur differences in gastric emptying under the conditions of the experiments presented here. In fact, in all models tested in these studies, the rate of D-xylose absorption was constant among groups, consistent with uptake starting at meal delivery and continuing through the course of observation. Hence, although D-xylose provides a surrogate for gastric emptying in human studies (36), it appears that acetaminophen, which is poorly absorbed in the stomach, is a superior nonradioactive indicator of gastric emptying in rats.

As expected, postmortem gastric pressure was elevated after VSG. To determine the extent to which increased gastric pressure contributed to faster emptying rates, we studied how various volumes of a viscous, noncaloric infusate affected gastric emptying in rats. To keep the conditions of the experiment as physiologically relevant as possible, volumes were chosen based on what rats consumed voluntarily (11, 43). Increased plasma levels of [14C]glucose with increased oral volumes in VSG rats are consistent with the notion that pressure effects contribute to faster gastric emptying. Our data are supported by multiple clinical studies that demonstrate that gastric pressure (50) and gastric emptying of liquids (2, 4), semisolids (29, 30), and solids (4, 27, 28, 40) are increased in patients with VSG compared with controls. What is surprising about these data is the extent to which these changes in nutrient handling overlap with RYGB.

Unlike sham-operated controls, VSG rats were unable to slow gastric emptying in response to increasing caloric densities of carbohydrate or fat. Pharmacological manipulation of muscarinic or GLP-1 receptors also failed to slow gastric emptying in VSG animals. Moreover, these effects were observed using a low-volume infusion that did not affect gastric emptying rate per se in VSG animals, implying that the removal of the gastric musculature and the neural networks contained within eliminates key factors that typically slow nutrient entry into intestine. There has been much speculation that rapid nutrient delivery directly into the midjejunum and beyond accounts for the tremendous increase in GLP-1 secretion after RYGB (12, 21, 25). Given the rapid gastric emptying that we observed in our study, the same could be hypothesized for VSG. In fact, we noted that both gastric emptying and plasma GLP-1 were greater in VSG animals given a gastric gavage of nutrients compared with shams. Interestingly, we found that increases in plasma GLP-1 also occurred when dextrose was infused directly into the duodenum of VSG animals, demonstrating that, in addition to faster gastric emptying, VSG results in intestinal effects that are independent of gastric function, possibly reflecting enhanced nutrient sensing at the level of the intestine. In support of this hypothesis, prandial levels of other hormones whose secretion is nutrient dependent are also increased after VSG, including PYY (14,
32, 33), cholecystokinin (32), gastric inhibitory polypeptide (44), and others (8, 14).

Limitations of our study include the focus on liquid nutrient and nonnutritive meals. Gastric digestion and emptying of solids are more complex and more prolonged. However, there are several advantages to studying gastric emptying in the liquid-phase. The labeling of solid meal components and lack of homogenous mixing of gastric contents can adversely affect measurements. Furthermore, the presence of a prolonged lag phase after solid meal ingestion can create situations in which the rate of gastric secretion may be greater than the rate of gastric emptying (15, 20). Secretion volumes are not trivial, especially given the sensitivity of VSG to volume-related increases in gastric emptying. Such confounds provide less than ideal conditions in which to study sensitive measurements of neural and endocrine influences on gastric emptying, as was the focus of our study. Moreover, others have already demonstrated that gastric emptying of solids is increased following VSG in humans (4, 28, 40) and in a rat (26) model of this procedure.

In summary, we report herein that animals with VSG and RYGB have similar and rapid gastric emptying compared with animals given a sham operation. Of the chemical techniques we used, acetaminophen may be the best indicator of gastric emptying in rodents since it can be done in conscious animals, is simple to perform, and requires minimal blood. Enhanced nutrient sensing and early satiety after VSG may be a physiological response to a perpetually faster gastric emptying rate. However, this hypothesis will need to be carefully evaluated. What is interesting is that despite the rapid nutrient entry into the system after VSG (and RYGB), overall glucose homeostasis is drastically and rapidly improved (1, 7, 8, 10, 18, 33). The sophistication of these outcomes challenges traditional explanations of VSG as a purely restrictive procedure.

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AUTHOR CONTRIBUTIONS

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