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Similar effects of roux-en-Y gastric bypass and vertical sleeve gastrectomy on glucose regulation in rats

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Abstract

Bariatric surgery is the most efficacious procedure for eliciting weight loss in humans, and many patients undergoing the procedure experience significant lessening of their symptoms of type-2 diabetes in addition to losing weight. We have adapted two bariatric surgical procedures commonly employed in humans to a rat model to begin to understand the mechanisms underlying the improvements in energy homeostasis. Young adult male rats received either roux-en-Y gastric bypass (RYGB) or vertical sleeve gastrectomy (VSG) and were assessed for body weight, food intake and parameters of glucose homeostasis over a 28-week period. Control rats received either a sham surgical procedure or else were unoperated. RYGB and VSG had comparable beneficial effects relative to controls. They ate less food and lost more weight, and they both had improved glucose parameters. The most intriguing aspect of the findings is that the two surgical procedures had such similar effects in spite of quite different rearrangements of the gastrointestinal system.

Keywords

Roux-en-Y gastric bypass (RYGB); Vertical sleeve gastrectomy (VSG); Bariatric surgery; Glucose tolerance; Insulin; GLP-1

The incidence of obesity continues to grow throughout much of the world, creating a tremendous burden in the form of associated health problems and enormous personal and societal expense [1]. Because the traditional therapeutic approaches of eating less while increasing physical activity are relatively ineffective in the long run for most individuals, more medically-based treatments have gained in popularity [2]. Pharmacotherapy, while mildly efficacious for some individuals, is bedeviled by undesirable side effects and long-term compliance issues, and only one compound (Xenical, which reduces the absorption of ingested fat) is currently approved to treat chronic obesity in the United States [3]. Bariatric surgery, in contrast, produces much larger reductions of weight and its use is increasing at an escalating pace [4,5]. This article summarizes some recent data on parameters of glucose homeostasis in two commonly used bariatric surgical procedures, roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG) using an animal model.

The rationale underlying bariatric surgery is that interference with the normal passage of ingested nutrients through the gastrointestinal (GI) tract will result in fewer nutrients actually entering the blood from the GI tract and ultimately result in reduced body weight

[6]. This might occur due to less food being voluntarily eaten, to less of the food that is eaten being absorbed through the intestinal walls, to less efficient processing of ingested nutrients, to other, as yet unknown, factors, or to any combination of these possibilities. There are myriad ways in which the normal routing of ingested food through the GI tract can be replumbed, and an ever-increasing variety of methods is being suggested and tried by surgeons [7]. We have developed a rat model of two commonly applied bariatric procedures in humans, RYGB and VSG, and we have begun to compare them head-to-head, or bowel-to-bowel, as the case may be.

Normally, ingested nutrients pass from the mouth through the esophagus and into the stomach, where the digestion process begins in earnest due to the actions of gastric secretions and mechanical mixing. When appropriately prepared, the partially digested mixture or chyme is then slowly passed through the pyloric sphincter separating the stomach from the first part of the small intestine, the duodenum. In the duodenum, pancreatic juice and bile are added to the chyme, and the mixture is moved along the small intestine through the jejunum and ileum and on to the large intestine via peristalsis. Digested nutrients can be absorbed into the body (via the blood or lymph) at any point along the small intestine. The non-absorbable contents of the chyme and other waste products leave the body via the rectum and anus.

In RYGB, the area of the stomach that connects with the esophagus is separated physically from the rest of the stomach, such that only a very small pouch remains to receive swallowed food. This small gastric pouch is then anastomosed to a section of the intestinal jejunum [7,8]. Hence, as food is eaten, the small functional gastric pouch is soon filled and the distension creates signals of discomfort that tend to cause smaller meals to be eaten. In addition, because the chyme then bypasses most of the stomach, the duodenum and part of the jejunum, there is a much shorter area of exposure of chyme to the intestinal wall, potentially limiting absorption of ingested nutrients. Hence, RYGB has the potential of being restrictive (smaller stomach) and malabsorptive (smaller absorptive area), as well perhaps as anorectic (earlier satiation).

In VSG, the volume of the stomach into which swallowed food enters from the esophagus is reduced by surgically shaping it into a narrow tube leading directly to the pyloric sphincter and duodenum; i.e., most of the stomach is disconnected from the tube of passage [9–11]. The intestines remain intact. Thus, VSG is characterized by restriction and perhaps anorexia. We chose to compare RYGB and VSG since both are commonly used clinically, both cause substantial weight loss, and both are associated with greatly lessened symptoms of type-2 diabetes mellitus and the metabolic syndrome [12–17]. Reports by others have documented the effects of RYGB in rats [18,19] and we have reported the effects of VSG [20].

1. Methods

Male Long–Evans rats (Harlan Laboratories, Indianapolis, IN; 250–300 g) were fed a high-fat butter oil-based diet (HFD; Research Diets, New Brunswick, NJ, D12451; 41% fat; 4.54 kcal/g) for 8 weeks prior to surgery; they became obese and hyperinsulinemic. For RYGB, a laparotomy was made and the jejunum was transected 30 cm from the ligament of Treitz and placed between 2 saline-moistened compresses. Exactly 10 cm distal to the transected bowel a side incision was made and connected to the afferent limb creating an end-to-side jejuno-jejunal anastomosis. The stomach was then isolated and loose connective tissue between the stomach and the spleen and liver was severed. The fundus was freed by cutting the suspensory ligament with the lower esophagus and excised by making a vertical cut along the edge of the corpus. A staple line was placed at an angle across the greater and lesser curvature creating a gastric pouch that was ~10% the size of the original stomach. The distal

remnant was returned to the peritoneal cavity and an incision was made on either side of the gastric pouch that spared the vascular architecture. The efferent limb of the transected jejunum was connected to the gastric pouch via a gastric-jejunal anastomosis. After reintegrating the gastric pouch into the peritoneal cavity, the abdominal muscles and dermis were closed in layers. Another group of rats (PF) received sham surgery and was pair-fed to match the daily intake of the RYGB rats.

For VSG, a laparotomy was made in the abdominal wall, allowing the stomach to be isolated outside the abdominal cavity and placed on saline-moistened gauze pads. Loose gastric connections to the spleen and liver were released along the greater curvature, and the suspensory ligament supporting the upper fundus was severed, thus widening the angle between the lower esophagus and the fundus. The lateral 80% of the stomach was excised using an ETS 35-mm staple gun, leaving a tubular gastric remnant in continuity with the esophagus superiorly and the pyloric sphincter and duodenum inferiorly. This gastric sleeve was then reintegrated into the abdominal cavity. Finally, the abdominal wall was closed in layers.

For sham RYGB surgery, a laparotomy was made in anesthetized rats and a section of jejunum was isolated and cut 30 cm beyond the ligament of Treitz. The two halves were then anastomosed end-to-end and the laparotomy was closed in layers. Sham VSG surgery involved abdominal laparotomy and placement of the stomach out of the abdominal cavity followed by manually applying pressure with blunt forceps along a vertical line between the esophageal sphincter and the pylorus of the stomach.

Following surgery, rats received intensive postoperative care for 5 days, consisting of twice-daily subcutaneous injections of 10 mL saline and 0.3 mL Buprenex. Rats were fasted 24 h prior to surgery and had free postsurgical access to Ensure Plus liquid diet (1.41 kcal/g; Abbott, Columbus, OH) until their regular diet was returned 3 days after surgery. Food and water intake were assessed daily, and various procedures were conducted beginning several weeks after surgery.

2. Results

All 4 groups (sham, RYGB, VSG and PF) had identical fat and lean masses as assessed by Echo MRI prior to surgery. All groups lost comparable and significant body weight during the first week following surgery (–8 to 10%). After that, the sham rats regained weight at a normal rate throughout the remainder of the experiment (28 weeks). Rats in the RYGB, VSG and PF groups continued to lose weight for 2–3 weeks following surgery, each group losing around 35% of its presurgical weight during that time. Rats in these groups then started gaining weight and were at ~70% of the weight of sham rats after 140 days; there were no significant differences of total body weight among the RYGB, VSG or PF groups over that interval (Table 1). The weight loss was predominantly due to a loss of body fat with a slight reduction of lean mass in all of these 3 groups relative to sham controls.

Food intake was initially suppressed in all surgical groups immediately after surgery. It returned to baseline levels within 1 week and then was relatively constant for the remainder of the experiment in the sham animals. Intake was initially suppressed further in the RYGB and VSG groups and required at least 3–4 weeks to increase to an asymptotic level. There was no difference in intake between the two operated groups at any time throughout the experiment.

Thus, both RYGB and VSG resulted in loss of body weight and body fat, and there was a concomitant significant decrease of plasma insulin (Table 1). Because these surgical

procedures are associated with improvements in diabetes in humans, we conducted meal and glucose tolerance tests on the rats.

Several months after surgery, rats were fasted for 6 h and then orally gavaged with 2.5 mL of Ensure-Plus Liquid diet, and blood samples were taken prior to and up to 1 h after treatment. There were no differences of fasting/baseline glucose among the 4 groups (Table 2). Blood glucose increased significantly by 15 min in sham rats and stayed elevated at around 200 mg/dL throughout the 60-min observation period (Table 2). A similar pattern occurred in the PF rats, although the post-gavage glucose levels were consistently lower than those in the sham rats, approaching an asymptotic level of around 175 mg/dL. By 15 min the blood glucose of both the RYGB and the VSG rats had risen to levels comparable to those in the sham animals; after that the glucose level of each decreased to a level around 150 mg/dL for the remainder of the experiment. Thus, although the integrated area under the glucose curve was similar for the RYGB, VSG and PF groups, the pattern was quite different, with an initial high increase followed by a rapid decline in the two operated groups (Table 2), and their patterns were very similar.

Fasting insulin was significantly higher in the sham rats (>3 ng/mL) than in any other group (PF=2 ng/mL; RYGB and VSG each ~ 1 ng/mL) (Table 1). Following the gavage, plasma insulin increased and then slowly returned toward baseline over the 60 min in the sham rats, ending at around 4 ng/mL. A parallel trend occurred in the PF group although the insulin levels were significantly lower at all time points. Fasting insulin levels were comparably and significantly lower than those in the PF rats for both the RYGB and the VSG rats, and these levels increased greatly at 15 min relative to the two control groups and then rapidly returned toward baseline, averaging between 1 and 2 ng/mL at 60 min. When taking glucose levels into account, both RYGB and VSG had significantly improved glucose tolerance with a far higher initial output of insulin; i.e., both surgeries resulted in greater initial insulin excursions from baseline with more rapid returns toward baseline, and a far greater insulin area-under-the-curve (AUC) (Fig. 1).

We also assessed plasma GLP-1(7–36) during the intragastric tolerance test. Sham and PF rats had comparable modest increments of GLP-1(7–36) over the 60 min. In contrast, RYGB and VSG rats secreted far more GLP-1(7–36), attaining plasma levels 5 to 6 times higher than in controls in both instances, and there were no differences in GLP-1 levels at any time point between the two groups (Fig. 2). The elevated GLP-1(7–36) in RYGB rats might be anticipated since the ileum is the source of most plasma GLP-1(7–36) and since the ingested food reaches the ileum so much sooner during meals due to the short-circuited route through the GI tract. This explanation may also account for the increased GLP-1(7–36) in VSG rats since there is compelling evidence that gastric emptying and transit are greatly accelerated after this surgery [21–23].

At 5 weeks after surgery, 6-h fasted rats were administered 50% dextrose (1.5 g/kg, ip). Glucose tolerance was improved in RYGB, VSG and PF groups relative to sham animals, although the area under the glucose curve attained significance relative to controls only in the PF rats (Fig. 3). Hence, the improved glucose tolerance must be attributed to the loss of body weight since there were no differences between the PF and the surgical groups in this regard.

3. Discussion and conclusions

Due in part to the failure of conventional behavioral methods to result in meaningful and sustained weight loss [2], and in part to a dearth of safe yet efficacious pharmaceuticals [3], bariatric surgery has become the therapy of choice for many obese humans, and especially those with type-2 diabetes or other severe metabolic disorders [4,5,15]. Although a number

of different surgical manipulations of the GI tract are being commonly employed, and many of them are quite successful, the underlying mechanism(s) of action is not known. An a priori assumption of many of the procedures is that making changes in the GI tract that reduce the amount of consumed energy being incorporated into the body must necessarily lead to a reduction of body weight. The validity of the assumption aside, the weight loss that does occur after procedures such as RYGB and VSG is most often attributed to a restricted gastric volume and/or a shorter/smaller area of exposure of nutrients to the absorptive intestinal surface.

We have directly compared RYGB and VSG using a model of high-fat diet-induced obese and hyperinsulinemic rats. As controls we had sham-operated rats as well as unoperated rats pair-fed to match the intake of operated animals. With the surgical parameters used in this experiment, the two bariatric surgery procedures (RYGB and VSG) caused comparable loss of body weight and body fat and both reduced plasma insulin. Both also caused comparable improvements of glucose tolerance and of GLP-1(7–36) secretion. What is surprising is that the spectrum of metabolic improvements was so comparable following RYGB and VSG despite such different surgical procedures. So whereas the cause(s) of the improvements cannot be ascertained from these experiments, it seems unlikely that specific alterations of the size of the stomach or specific rerouting of the chyme through the intestines is a key. Rather, common endocrine or other changes resulting from the surgical procedures must be invoked.

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Fig. 1.

15-min insulin excursions expressed as a change from baseline during the mixed meal tolerance test. RYGB and VSG produced similar increases in postprandial insulin release that were much greater than changes in sham or PF rats. Bonferroni's post-test; \$ $P < 0.05$ vs. RYGB, # $P < 0.05$ vs. VSG, * $P < 0.05$ vs. PF.

Fig. 2.

Mean blood glucose levels (mg/dL) calculated as AUC after I.P. glucose. Compared to ad lib-fed sham (n=10) rats, RYGB (n=4), VSG (n=7), and PF (n=10) rats had lower glucose excursions and did not differ among themselves. Bonferroni's post-test; * $P < 0.05$ vs. PF.

Fig. 3.

Levels of active plasma GLP-1(7–36) shown as AUC during the mixed meal tolerance test. GLP-1(7–36) levels were significantly higher in RYGB and VSG rats relative to sham and pair-fed animals, $P < 0.05$. Differences between sham and pair-fed rats were not significant, $P > 0.05$. Bonferroni's post-test; \$ $P < 0.05$ vs. RYGB, # $P < 0.05$ vs. VSG, * $P < 0.05$ vs. PF.

Table 1

Body weight and fasting plasma insulin levels in sham (n=7), RYGB (n=4), VSG (n=6), and PF rats (n=10).

	Sham	RYGB	VSG	PF	ANOVA
<i>Body wt (g)</i>					
Pre-surgery	543±17	556±21	538±13	541±15	<i>P</i> =0.93
5 mo post-op	767±33 ^{*,\$,#}	549±33	531±18	580±12	<i>P</i> <0.0001
<i>Insulin (ng/mL)</i>					
5 mo post-op	3.2±0.22 ^{*,\$,#}	1.0±0.11	1.3±0.09	2.0±0.18	<i>P</i> <0.0001

Bonferroni's post-test;

^{*} *P*<0.05 vs. PF,

^{\$} *P*<0.05 vs. RYGB,

[#] *P*<0.05 vs. VSG.

Table 2

Blood glucose levels (mg/dL) before (Time 0) and after an oral gavage of Ensure-Plus liquid diet in sham (n=8), RYGB (n=6), VSG (n=6), and PF (n=9) rats. Blood glucose levels were significantly lower in RYGB and VSG rats relative to ad lib fed sham animals after 45 and 60 min, $P<0.05$.

	Sham	RYGB	VSG	PF
0 min	114±5.6	103±3.2	118±4.0	108±3.8
15 min	182±11.3	181±14.7	187±11.6	154±5.3
30 min	181±15.2	152±12.3	152±7.2	163±5.3
45 min	197±16.7 ^{§,#}	151±6.7	146±4.7	178±5.1
60 min	209±15.2 ^{§,#}	161±8.1	151±7.5	180±6.0

Bonferroni's post-test;

[§] $P<0.05$ vs. RYGB,

[#] $P<0.05$ vs. VSG.