All Bariatric Surgeries Are Not Created Equal: Insights from Mechanistic Comparisons

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Despite considerable scientific progress on the biological systems that regulate energy balance, we have made precious little headway in providing new treatments to curb the obesity epidemic. Diet and exercise are the most popular treatment options for obesity, but rarely are they sufficient to produce long-term weight loss. Bariatric surgery, on the other hand, results in dramatic, sustained weight loss and for this reason has gained increasing popularity as a treatment modality for obesity. At least some surgical approaches also reduce obesity-related comorbidities including type 2 diabetes and hyperlipidemia. This success puts a premium on understanding how these surgeries exert their effects. This review focuses on the growing human and animal model literature addressing the underlying mechanisms. We compare three common procedures: Roux-en-Y Gastric Bypass (RYGB), vertical sleeve gastrectomy (VSG), and adjustable gastric banding (AGB). Although many would group together VSG and AGB as restrictive procedures of the stomach, VSG is more like RYGB than AGB in its effects on a host of endpoints including intake, food choice, glucose regulation, lipids and gut hormone secretion. Our strong belief is that to advance our understanding of these procedures, it is necessary to group bariatric procedures not on the basis of surgical similarity but rather on how they affect key physiological variables. This will allow for greater mechanistic insight into how bariatric surgery works, making it possible to help patients better choose the best possible procedure and to develop new therapeutic strategies that can help a larger portion of the obese population. (*Endocrine Reviews* 33: 595–622, 2012)

I. Introduction: Obesity, an Expanding Problem

The control of energy balance is no longer a complete mystery. Over 30 yr ago, Coleman's parabiosis experiments made the discovery of leptin possible, leading to the continued unraveling of the enigma surrounding the

Abbreviations: AGB, Adjustable gastric banding; AgRP, agouti-related peptide; ARC, arcuate nucleus; BMI, body mass index; CCK, cholecystokinin; CNS, central nervous system; GB, nonadjustable gastric banding; GI, gastrointestinal; GLP, glucagon-like peptide; GOAT, ghrelin *O*-acyltransferase; HDL, high-density lipoprotein; HG, horizontal gastroplasty; JIB, jejuno-ileal bypass; LDL, low-density lipoprotein; MC4, melanocortin 4; MC4R, MC4 receptor; NPY, neuropeptide Y; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY; RQ, respiratory quotient; RYGB, Roux-en-Y gastric bypass; VBG, vertical banded gastroplasty; VSG, vertical sleeve gastrectomy.

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regulation of body weight. Despite these important scientific advances, the treatment of obesity continues to be a major challenge. Obesity is now pandemic in the United States as well as in other nations. In the United States, it is now more common to be overweight than not; over two thirds of the population meet criteria for overweight, and over one third are obese (1). This is an expensive problem. The annual individual cost of being obese in this country has been estimated at $4879 for women and $2646 for men, not including the cost of years lost due to obesity (www.gwumc.edu/sphhs/departments/healthpolicy/pdf/heavyburdenreport.pdf). The U.S. government spends an estimated $147 billion yearly on obesity-related costs alone (3).

The heart of this problem is that few effective therapeutic options are available to the obese patient. Traditionally, diet and exercise have been used as primary modes of treatment for obesity. The drawback to this strategy, however, is that for most individuals, it does not produce sustained weight loss. Dieting is associated with only modest amounts of long-term weight loss (4–6). In one representative study (6), less than 20% of individuals who had attempted to lose weight were able to achieve and maintain weight loss of 10% over 1 yr. Difficulty maintaining long-term weight loss reflects the strongly conserved nature of the homeostatic regulatory mechanisms protecting body weight (7). So despite our rapidly growing understanding of energy balance regulation, our efforts to turn that knowledge into treatments have been met with minimal success. This is evidenced by the fact that the approved pharmaceutical options for weight loss are restricted to a single agent with limited efficacy (8).

II. Bariatric Surgery: New Promise for the Treatment of Obesity?

Given this relatively bleak picture, it is not surprising that bariatric surgery has increased in popularity due to its ability to produce long-term weight loss that is superior to traditional weight loss treatments in both magnitude and durability. Additionally, some bariatric procedures reduce overall mortality despite the inherent risks of surgery itself (9, 10), an effect that is perhaps due to the superior ability for bariatric surgery among weight loss treatments to induce long-term metabolic benefits. Reduced incidence of diabetes (11), heart disease (12), and cancer (13) have been reported in individuals who have received bariatric surgery. The effects on some of these elements are powerful enough that for some patients pharmacological treatment for diabetes and other elements of the metabolic syndrome such as hyperlipidemia and hypertension can often be discontinued after surgical treatment (14).

The first weight loss surgeries were performed in the 1950s by Drs. Mason and Ito (15). The earliest procedure, the jejuno-ileal bypass (JIB) surgery, redirected nutrient flow to bypass most of the small intestine and was intended to produce weight loss by malabsorption. Because of a severe syndrome of complications including arthritis, skin problems, and liver failure that occurred after this procedure, JIB is no longer used. Later, in 1967, Mason and Ito (16) introduced a gastric bypass procedure that produced weight loss without these side effects. This procedure was based on the weight loss observed after partial gastric resection for the treatment of gastric ulcers. This procedure involved the creation of a small stomach pouch connected to a limb of distal intestine, bypassing the proximal intestine. The contemporary Roux-en-Y gastric bypass (RYGB) procedure is a modification of this early procedure. The RYGB has a much smaller gastric pouch size than Mason and Ito's original procedure, and the intestinal component of the surgery has been modified to avoid bile reflux, but the basic principle remains the same. Another currently used bariatric procedure is adjustable gastric banding (AGB), a restrictive procedure in which a saline-filled silicon band is fitted around the stomach near the esophageal junction (17). The level of gastric restriction imposed by the band may be adjusted by infusing saline via a sc port. Together, AGB and RYGB are the two most commonly performed bariatric procedures (18).

Vertical sleeve gastrectomy (VSG), another procedure that has received increasing attention over the past decade, involves the removal of 80% or more of the stomach, including the fundus and greater curvature. VSG was first described in 1998 as a part of the biliopancreatic diversion-duodenal switch procedure (19). It has since been used alone as a staging procedure in super-obese patients [body mass index (BMI) > 50 kg/m^2] (20–24) due to its lack of invasiveness and to its ability to produce significant weight loss. Increasingly, VSG is gaining popularity as an independent weight loss procedure for all degrees of obesity. The procedure is attractive as a single-stage weight loss intervention because it entails less surgical risk and reduced postsurgical complications. Additional benefits include the maintenance of an open pathway for future endoscopic studies, the lack of need to implant foreign material that may fail, and low risk for malabsorption of either fat-soluble vitamins or drugs. Complication rates range from 0–24% for VSG, and the procedure has an overall mortality rate of 0.39% (25).

Increasing evidence highlights VSG as a procedure that can produce substantial weight loss comparable to that produced by more invasive and complex procedures like

RYGB. A recent meta-analysis (26) directly comparing studies of VSG, RYGB, and AGB demonstrated similar weight loss after RYGB and VSG that was superior in magnitude and durability to the weight loss induced by AGB. Despite a rapidly expanding body of data surrounding these surgeries, it is yet unclear what physiological mechanisms underlie the ability for each surgery to produce sustained weight loss as well as metabolic improvement.

The choice of several different bariatric procedures, including RYGB, VSG, and AGB, presents many unanswered questions for the obese patient considering surgical treatment, necessitating a deeper understanding of these procedures. The increasing popularity of bariatric surgery and the recent development of rodent models for these procedures, however, have given impetus to the field of research around mechanisms for surgically induced weight loss. This review focuses on mechanisms for weight loss after VSG, RYGB, and AGB. A key element of this discussion will be a direct comparison of the dynamic physiological changes that occur after each of these procedures. Our aim is to help define mechanisms for weight loss and metabolic improvement after each surgery and to promote a greater understanding of how the gastrointestinal (GI) tract contributes to the regulation of energy balance and other physiological processes critical to the metabolic syndrome. The long-term goals of such research are 2-fold: 1) to help identify which patients should receive which (if any) procedure and 2) to develop more efficient, cost-effective, and less invasive procedures and other therapeutic strategies that provide similar weight loss and metabolic benefits.

III. Metabolic Benefits beyond Weight Loss

A. Lipid homeostasis and cardiovascular risk reduction

A significant cause of mortality in obese patients is cardiovascular disease. Cardiovascular disease is the leading cause of death in the general U.S. population (27), but severe obesity increases this risk by as much as 3-fold (28). High triglycerides, reduced levels of high-density lipoprotein (HDL) cholesterol, and abnormal low-density lipoprotein (LDL) composition are characteristic of obesity-related dyslipidemia (29).

A powerful effect of bariatric surgery is not only to reduce body fat but also to elicit improvement to other metabolic parameters such as glucose tolerance and plasma lipids. One study reported improved plasma lipid profiles in at least 70% of a mixed cohort of bariatric surgery patients after restrictive and malabsorptive surgeries (30). Specifically, improvements have been documented in humans after RYGB (31), AGB (32), and VSG (33). Despite these improvements, it is clear that certain bariatric procedures are more effective than others to reduce dyslipidemia. Improved HDL levels have been reported after all three procedures (32, 34, 35), but the relative degree of improvement after each surgery has not been compared. Large, prospective human and/or animal studies comparing VSG, RYGB, and AGB will be necessary for such a comparison. However, literature comparing RYGB and either VSG or AGB appears to position RYGB as a surgery unique in its ability to reduce total cholesterol and LDL levels (34, 35). It is unclear what mechanisms may underlie these unique effects of RYGB, but they appear to be weight independent; RYGB elicited weight loss that was superior to AGB (34) but comparable to VSG (35). Intestinal lipid malabsorption can occur after RYGB (36, 37). However, most surgical variants of this procedure minimize this effect, and it seems unlikely that malabsortion is a major contributor to the reduction in plasma total cholesterol levels in the majority of RYGB patients. Furthermore, no studies have directly compared the effects of RYGB *vs.* VSG or AGB on either fecal or plasma lipid composition, and it is unknown how RYGB might affect *de novo* cholesterol synthesis to influence plasma cholesterol levels.

RYGB causes similar reductions in plasma triglycerides compared with VSG (35) but is superior to AGB (34). It is unclear whether VSG and RYGB might act via similar mechanisms to reduce triglyceride levels, but a key question is whether improvement of dyslipidemia after bariatric surgery might occur independently of weight loss. Animal studies provide the opportunity to answer such questions much more readily than in human research. Recently, our group found that VSG in rats produces a dramatic, weight-independent reduction in plasma triglyceride levels (38). Surprisingly, this reduction is due to reduced postprandial trigylceride secretion from the intestine into the circulation and is not due to intestinal lipid malabsorption (38). Given the more dramatic change in plasma lipids but similar weight loss (35) after RYGB compared with VSG, it might be hypothesized that RYGB also produces weight-independent changes to lipid homeostasis, perhaps at the level of the intestine. An important aspect of these studies will be to investigate the potential contribution that impaired fat absorption might make to lipid homeostasis after RYGB. Most importantly, focusing on intestinal physiology after these procedures should elucidate mechanisms that are common among these bariatric procedures *vs.* those that explain the unique effects of the individual surgeries.

B. Glucose homeostasis

Along with improved lipid profiles, some bariatric surgeries result in drastic improvements to glucose homeostasis. Improved glucose homeostasis may be mediated by changes to insulin secretion or insulin sensitivity. Patients with abnormal glucose tolerance typically have higher insulin levels after glucose administration, a response that is a compensation for reduced insulin sensitivity. Prediabetes and type 2 diabetes represent a spectrum along which the glucose-induced insulin response becomes inadequate. As the disease progresses, β-cell mass is reduced and β-cells eventually fail to secrete insulin.

Both insulin secretion and sensitivity improve with weight loss. This is also the case after bariatric surgery, but the effects may occur sooner than expected for weight loss. Fasting glucose concentrations have been reported to be reduced before substantial weight loss after RYGB (39, 40) and VSG (41, 42). Indeed, it has been reported that aberrant glucose levels can be reduced in less than 1 wk after surgery (39, 41, 42). In a large study of 1160 patients, one third of patients requiring either insulin or oral antidiabetes agents before surgery were able to discontinue these medications before discharge, with a median stay of 3.3 d (43). The rapidity of these effects has been taken as evidence that glucose regulation improves independently of the weight loss produced by these procedures (44, 45). However, no studies have looked directly at oral glucose tolerance after either RYGB or VSG. As a result, the early improvements in oral glucose tolerance may be overstated, and studies that directly test this claim are needed.

In contrast to what data might suggest for RYGB and VSG, improvements in glucose regulation after AGB appear to be entirely dependent upon weight loss (46). In 2006, Korner *et al.* (46) assessed the effect of RYGB and AGB on glucose tolerance in patients that were matched for BMI and duration after surgery and found that RYGB produced a rapid decline in postprandial glucose excursions that was not seen in patients that underwent AGB. As it turns out, similar effects have been demonstrated after VSG. In 2010, Abbatini *et al.* (47) used a hyperinsulinemic-euglycemic clamp, the most sensitive technique available to measure insulin sensitivity, to show that, in type 2 diabetic patients, the relative increase in whole-body insulin sensitivity after VSG was comparable to that produced by RYGB. In both VSG and RYGB, the increase in insulin sensitivity was greater than that seen in AGB patients.

In our rodent models of RYGB and VSG, we used a radioactive tracer combined with the hyperinsulinemic-euglycemic clamp to assess tissue-specific effects of these surgeries. We found that RYGB and VSG had comparable and potent effects to increase hepatic insulin sensitivity beyond the improvement produced in pair-fed rats with comparable weight loss just 14 d after surgery (48). Hepatic glucose production is a key metabolic process that is increased in type 2 diabetic patients, contributing to their hyperglycemia. The effect of RYGB and VSG on hepatic insulin sensitivity likely explains at least part of the weight-independent benefit of these surgeries on glucose tolerance reported in our own study (48) as well as others (49, 50).

Changes in insulin secretion secondary to improved β-cell function could improve glucose homeostasis either together with, or independent of, insulin sensitivity. Unfortunately, the wide array of available techniques, some fraught with interpretive issues, brings us no closer to understanding of short- *vs.* long-term β-cell adaptations to surgery. Interpretation of clinical studies using glucose and/or insulin responses to an oral glucose load to get an indication of β-cell function (51, 52) are complicated by the fact that RYGB accelerates gastric emptying (see *Section IV.C, Gastric emptying*). This alters peak glucose levels, which are used by many modeling calculations typically used to estimate insulin secretion. For example, one study that used insulin and glucose levels 30 min after an oral glucose load found that this estimate of β-cell function was impaired after RYGB (52). However, these same patients had an improvement in the disposition index, a calculation that takes into consideration insulin secretion and sensitivity (52). Similarly, Nannipieri *et al.* (51) used mathematical modeling of glucose and insulin responses to oral glucose to show that diabetic RYGB patients with early remission tended to have the highest β-cell glucose sensitivity. An iv glucose tolerance test might be a more appropriate technique to study insulin secretion, and two recent studies have both reported an improvement in insulin response to an iv glucose load 6 months (53) and 1 yr (54) after RYGB surgery. The gold standard for examining insulin secretion is via the use of a hyperglycemic clamp. In this technique, all subjects have glucose levels clamped at similar elevated levels and the insulin response is examined. At the time of this review, only one study has used this technique in bariatric surgery patients, and although the main purpose of the study was not the influence of RYGB on insulin secretion *per se*, they did see that RYGB patients had elevated insulin levels during the clamp compared with BMI-matched control subjects. Regardless of all of this, it is possible that baseline β-cell function could be predictive of which patients will have diabetes remission after surgery (51, 55).

Although the use of the glycemic clamp techniques allows us to separately examine the impact of these surgeries on insulin sensitivity and secretion, the intestinal adaptation to these surgeries likely contributes to the mechanisms

underlying improvements in glucose homeostasis. For example, changes in gut hormones, including glucagon-like peptide (GLP)-1, gastric inhibitory peptide, peptide YY (PYY), and amylin, are often implicated as a mechanism for the weight-independent effects of VSG and RYGB (48, 56) surgeries on glucose homeostasis. This is in part because nonsurgical weight loss (50, 57) and purely restrictive procedures such as the AGB have little or no effect on postprandial hormone profiles. In contrast, human and rodent studies have demonstrated increased GLP-1 and PYY after RYGB and VSG (40, 48, 49, 56–59), and these hormones have favorable effects on insulin sensitivity (60, 61).

IV. Mechanisms for Metabolic Benefits of Bariatric Surgery

A. What causes reduced food intake?

Although JIB and, later, RYGB were developed with the intention of creating malabsorption, research indicates that it is a reduction in food intake, rather than malabsorption, that is the primary impetus for the negative energy balance and accompanying weight loss after RYGB, VSG, and AGB (48, 62, 63, 65). Pair-feeding studies have shown that nonoperated animals that are allowed to consume only as many calories as bariatric-operated rats lose the same amount of weight (38, 48, 62, 65). However, it is not known which mechanisms are important for the reduced food intake after each surgery or whether each surgery does so in a distinct way. One hypothesis is that gastric volume reduction, a common element of RYGB, VSG, and AGB, restricts food intake by physical means. Although this argument is appealing, we argue that the superior durability of the VSG and RYGB *vs.* AGB stems from other permanent physiological changes that reduce food intake despite the ability to overeat. Several lines of evidence support this argument.

B. Gastric volume restriction

Like AGB, VSG has conventionally been thought to elicit weight loss by physically restricting gastric capacity (66–70). Due to reduced stomach size and removal of the highly distendable gastric fundus, a given volume will increase pressure much more quickly in the gastric sleeve as compared with an intact stomach (70). Thus, it has been widely hypothesized that increased gastric pressure triggers earlier satiety after VSG. This restrictive dogma, however, has been challenged by recent data from both humans and rodents after VSG.

Melissas *et al.* (71) assert that VSG should not be viewed as a restrictive procedure. To support their argument, the authors highlight that the volume of the stomach remaining after VSG in humans (about 150–200 ml) (72) is much larger than the volume remaining after gastric banding (typically 15–20 ml) (17), whereas weight loss observed after VSG is greater than after AGB. Furthermore, VSG produces weight loss and glycemic improvement that are more comparable to what is achieved by RYGB (66).

Band malfunction (insufficient stomach restriction) after AGB leads to weight regain (73–75). In contrast, gastric dilation after VSG does not necessarily abrogate weight loss. Gastric dilatation is not common after VSG, estimated to occur in only one of 14 patients 1 yr after surgery (66), but when it does occur, it is unlikely to limit surgical success (66, 72). Furthermore, gastric tube size does not predict excess weight loss in humans (76).

Data exploring the relationship between gastric size and weight trajectory are only associative reports. Development of bariatric surgeries in animals has made it much easier to directly test potential causal relationships between stomach volume and weight loss. At present, this relationship has been studied most extensively in VSG among bariatric surgeries. In VSG-operated rats, after an initial period of hypophagia during which substantial body weight loss is achieved, daily caloric intake returns to presurgical levels. This indicates that despite the greatly reduced stomach volume, normal intake can be achieved. More importantly, refeeding after a period of caloric restriction leads to the gain of body weight by increasing intake above what was consumed before the surgery. The result is that VSG-operated animals quickly attain their prerestriction body weight while maintaining the reduced body weight associated with the effect of the surgery (Fig. 1, from Ref. 62). Hence, VSG-operated animals have the ability to increase food intake to gain body weight. Nevertheless, they do not use this ability to regain the lost weight from the surgery even while they will use this ability to fend off the effects of caloric restriction. This is contrary to unoperated diet-restricted rats, who will compensate for lost body weight by exhibiting hyperphagia until body weight is restored (77). Thus, compared with dieting, VSG is unique in that it is not associated with rebound hyperphagia. This point is critical to the understanding of VSG-induced weight loss, because it implies that some physiological changes, including satiety, are caused by the surgery that make it quite unlike the biological and behavioral results of food restriction.

There are no reports that ask whether RYGB-operated animals are able to increase food intake beyond their postsurgical baseline. However, Zheng *et al.* (78) have dem-

Figure 1.

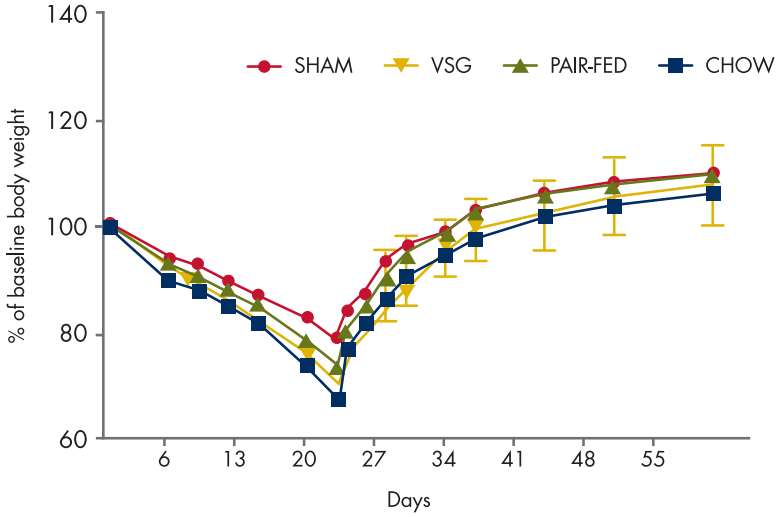


Figure 1. Refeeding after an extended period of caloric restriction is associated with identical rate and magnitude of body weight regain in sham-operated rats fed either high-fat diet HFD (SHAM) or chow, pair-fed rats, and VSG-operated rats. No significant differences between groups. To accomplish this, all groups (including the VSG-operated rats) eat more calories after the restriction than in the baseline period before the restriction. [Data from Stefater MA *et al.*: Sleeve gastrectomy induces loss of weight and fat mass in obese rats, but does not affect leptin sensitivity. *Gastroenterology* 138:2426, 2010 (62), with permission. © Elsevier.]

onstrated that RYGB-operated rats consume much smaller and more frequent meals than sham-operated controls, a pattern that is consistent with what is seen after VSG (62).

Another argument against gastric volume reduction as the primary driving force for reduced caloric intake comes from data on food choice in bariatric patients and animals (discussed in more detail in *Section VI*, *Ingestive Behaviors*). If weight loss depended only on caloric restriction secondary to an inability to increase meal size and/or frequency, then one would expect that these animals would compensate by selecting the most calorically dense diet available to maximize the number of calories in their small stomachs. In fact, VSG- and RYGB-operated rats exhibit exactly the opposite pattern, selecting less fat (which is more calorically dense than carbohydrate or protein) and increasing their preference for diets of lower caloric density (79).

The important point is that despite the anatomical differences between VSG and RYGB, they produce common changes in ingestive behavior, and those changes are not easily linked to the mechanical effects of a smaller stomach. Rather, they suggest other common underlying physiological effects of VSG and RYGB that drive the sustained behavioral changes and that these effects may not be shared with AGB.

C. Gastric emptying

Because VSG, RYGB, and AGB are surgeries that affect stomach volume, it has been hypothesized that altered gastric emptying might be important for the ability of these procedures to affect satiety. Delayed gastric emptying has been proposed to reduce hunger by increasing gastric volume and pressure. Afferent vagal fibers lining the stomach (80, 81) and small intestine (82) express stretch receptors, and so it has been proposed that gastric stretch might elicit satiety (83). Improved satiety after bariatric procedures has been hypothesized to occur secondary to delayed gastric emptying. Contrary to this argument, ABG does not alter total gastric emptying but enhances emptying of the proximal gastric pouch created by the band (84). Emptying of this proximal pouch is most likely to affect satiety because the pressure within this pouch is highest and most altered by a meal, but no correlation links satiety or weight loss to gastric emptying rate after ABG (85).

Surgical manipulation of the GI tract in RYGB leaves no functioning pylorus, thus leaving no valve mechanism for metering entry of nutrients into the intestine. However, one report has actually shown a delay in gastric emptying and an increase in intestinal transit time after RYGB (86). Meal composition and/or consistency might also be a critical variable, because liquids have been shown to elicit more rapid gastric emptying than solids in RYGB patients (87). Interestingly, after VSG, a surgery that maintains pyloric function, most reports suggest an increase in gastric emptying (71, 88, 89). One report has shown an increase in intestinal transit time (89). There is another report of an antrum-sparing VSG that did not alter gastric emptying rate (90). These apparent inconsistencies in the data regarding gastric emptying after VSG might be explained by differences in surgical technique or bougie size, because very small pouch size might actually impair gastric emptying (91), or by failure to distinguish between diabetics and nondiabetics in an obese study population, because diabetes can affect GI motility (88).

Altered gastric emptying after these procedures could be a response to endocrine and/or neural mechanisms. One might predict that attenuated gastric emptying after these procedures might be due to enhancement of the pyloric brake mechanism that occurs secondary to enhanced enteroendocrine action stimulated by increased nutrient

delivery to the distal small intestine. Vagal tone is another factor that might contribute to altered gastric emptying after surgery. Due to anatomical differences between RYGB, VSG, and AGB, disruption of vagal fibers to the stomach during each surgery might follow distinct patterns contributing to differences in gastric emptying. This may also involve disruption of vagally mediated effects on the release of substances from gastric mucosa that inhibit gastric emptying. An example is gastrin, which is secreted by a vasovagal reflex in response to antral distension (92). Additionally, vagal remodeling, which is known to occur after chronic fundal ligation (a procedure similar to AGB) (93), may contribute to emptying rate. Regardless of the mechanism, it is interesting to speculate that the increased gastric emptying rate could increase delivery of nutrients to enteroendocrine cells in the distal gut, contributing to some of the physiological similarities between VSG and RYGB discussed in *Sections V.D. and V.E.* If this is true, then understanding the metabolic impact of rapid delivery of nutrients to the small intestine will be critical to understanding the mechanisms responsible for improvements to both glucose and lipid homeostasis after surgery.

D. Central nervous system (CNS) control of energy balance

Body weight maintenance is dependent upon the brain's ability to respond to internal cues relaying information about both long-term and short-term energy availability. Durable weight loss after bariatric surgery is therefore hypothesized to be due to interaction with CNS homeostatic circuitry.

The arcuate nucleus (ARC) of the hypothalamus is a key component of this homeostatic system. The ARC is composed of two neuronal populations thought to be important effectors of hormonal and local fuel signaling. The first population contains catabolic proopiomelanocortin (POMC)-producing neurons. POMC mRNA expression is increased in the ARC after administration of leptin or insulin (94–96). POMC is cleaved to produce α-MSH, a hormone whose role in peripheral cells is to regulate skin and hair pigmentation but which decreases food intake and induces weight loss when administered exogenously (97, 98). This effect is thought to be mediated by the melanocortin 4 (MC4) receptor (MC4R) subtype, found concentrated in the hypothalamus. Increased food intake and body weight in *MC4*-knockout animals (99) suggest a role for the endogenous stimulation of MC4R by α-MSH to affect energy balance. The identification of causative genes both for rare, monogenic forms of obesity as well as genome-wide association scans comparing obese *vs.* lean individuals have also supported a role for disrupted melanocortin signaling to promote obesity (100).

A second population produces the anabolic transmitters neuropeptide Y (NPY) and agouti-related peptide (AgRP). AgRP is found exclusively in the ARC and acts as a competitive antagonist/inverse agonist at MC4R (101). During times of energy deficiency, AgRP blocks the catabolic effects of α-MSH, resulting in increased food intake and weight gain. Indeed, exogenous AgRP administration or genetic *AgRP* overexpression has been shown to produce weight gain and to stimulate food intake (102, 103). However, genetic disruption of *AgRP* has no effect on either food intake or weight gain (104). Like AgRP, NPY stimulates food intake and weight gain (105, 106) and is produced in the same ARC neurons as AgRP.

The MC4R is found in several brain regions, including hypothalamus, forebrain, and hindbrain (107, 108). One such area is the paraventricular nucleus (PVN), which appears to be a center for integration of signals from multiple brain regions involved in the regulation of food intake and body weight. Site-specific injection of an MC4R agonist such as melanotan-II or α-MSH into the PVN elicits an anorectic response (109–111); conversely, local administration of an MC4R antagonist such as AgRP, SHU9199, or HS014 stimulates feeding (109–112). Either response is observed only after feeding has been initiated, for example by the onset of the dark cycle, and therefore it is hypothesized that PVN MC4 signaling is involved in the regulation of meal duration rather than of meal initiation (113).

Given the importance of central melanocortin signaling to regulate body weight, it has been hypothesized that the success of bariatric surgery as compared with diet and exercise may result from changes to this axis that reset the body's homeostatic machinery. Although this has not been directly tested for VSG, current data do not support a role for enhanced melanocortin signaling to explain weight change after these procedures. *POMC*, *AgRP*, and *NPY* expression in mediobasal hypothalamic samples does not differ between VSG-operated, sham-operated, obese rats, or lean pair-fed rats (62). Because the expression of these genes was assayed both during the phase of rapid postoperative weight loss and during the weight maintenance phase after weight loss, melanocortin signaling is not expected to explain either the superior magnitude or longer duration of weight loss after VSG surgery, as compared with caloric restriction alone. The same may be said for RYGB, which is effective even in individuals with heterozygous mutations in the gene encoding the MC4R (114). Two studies have investigated whether AGB failures might occur more frequently in individuals with *MC4R* mutations. Although an early study supported this hypothesis (115), a more recent study (116) failed to find *MC4R* mutations in any of 35 failed cases. This latter evidence seems to suggest other, extrahypothalamic mech-

anisms responsible for cases of AGB failure. However, no studies have directly measured hypothalamic *POMC*, *AgRP*, or *NPY* expression after either gastric band or RYGB surgery. Although current evidence seems to argue that changes to central melanocortin activity is not the primary mechanism for weight loss and maintenance after VSG, vertical banded gastroplasty (VBG), or RYGB, additional studies will be important to profile hypothalamic changes after these surgeries and to determine whether melanocortin signaling might contribute to the observed changes in energy balance. Performing these surgeries in genetically manipulated animals, especially *MC4R*-knockout mice, will be critical to provide definitive answers to these questions.

E. Energy expenditure

Energy expenditure is half of the energy balance equation, and so its potential contribution to energy balance after bariatric surgery should not be ignored. Caloric restriction in obese humans (117) and rats (118) is associated with a compensatory decrease in energy expenditure, contributing to the difficulty of losing weight by dieting. Augmented energy expenditure after bariatric surgery might therefore confer significant advantage of surgery over lifestyle interventions to treat obesity.

Interpreting energy expenditure is tricky, given the rapid changes in body weight and body surface area that occur after bariatric surgery. Whether patients after RYGB or VSG show the decreased energy expenditure that would be expected from their weight loss is controversial. The bulk of the human data concludes that RYGB decreases energy expenditure (119–122). Controversy remains for two reasons. First, it is quite difficult to compare humans (or rodents) of different weights and body compositions on their relative rates of energy expenditure (see Ref. 123 for a review of these problems). No consensus exists regarding the relative accuracy of normalizing oxygen consumption to body weight, body surface area, or lean body mass. Perhaps for this reason, literature exists both to support (124, 125) and to refute (120) increases in energy expenditure after RYGB. Two recent animal studies (78, 126) highlight this controversy. Stylopoulos and colleagues (126) show that RYGB increases both total and resting oxygen consumption in rats, as calculated by dividing oxygen consumption by body weight$^{0.75}$. This change in energy expenditure has been hypothesized to reverse obesity-related metabolic suppression, because RYGB enhanced energy consumption as compared with both calorically restricted, high-fat diet-fed and lean, chow-fed rats. Consistent with this finding, uncoupling protein 2 is increased in adipose tissue after RYGB in rats (127). Data from another group (78), however, challenge the relevance of these differences. Although in this study, RYGB did exhibit a tendency to increase energy expenditure when normalized to body weight, the effect was diminished when data were normalized either to body weight$^{0.75}$ or to lean body mass.

The second reason that it is difficult to reach an absolute conclusion about RYGB's effects on energy expenditure in humans is the need to compare with subjects who have lost weight by other means. Weight loss will decrease energy expenditure, and consequently, the key question is not whether energy expenditure is decreased on an absolute basis but rather whether the amount of reduction seen after RYGB is the same as it would have been after a large weight loss imposed in another manner. The rodent data lead us to hypothesize that it is likely that the reduction in energy expenditure will not be appropriate to explain the large observed level of weight loss. This perspective remains controversial, but direct comparison studies are in progress, and so a data-driven answer should be available in the future.

After VSG in rats, we observed no decrease in energy expenditure, which would be expected after substantial weight loss (62). As a newer procedure, no reports have measured energy expenditure after VSG in humans. However, it has been argued that energy expenditure does not drive weight loss after VSG, because pair-fed animals exhibit similar rates of weight loss (62). Thus, our interpretation of the rodent data is that RYGB (and potentially VSG), but not AGB, blunts the expected reduction in energy expenditure associated with negative energy balance. Energy expenditure after AGB has not been reported, but we hypothesize that it will not demonstrate this protective effect.

The recent development of rodent models of bariatric surgery has made it much easier to study and compare changes to energy expenditure after each surgery. One advantage to animal studies is that, by including specific dietary controls, they allow for measurement of nutrient use. Enhanced energy expenditure in the previously mentioned animal study (126) was nutrient dependent, because increased oxygen consumption in RYGB-operated animals disappeared during fasting (126). Respiratory quotient (RQ) in this study was reduced in RYGB-operated animals as compared with obese controls, indicating greater fat utilization. This difference disappeared during refeeding after a 48-h fast, reflecting accelerated RQ increase upon initiation of feeding in RYGB-operated rats as compared with their obese counterparts. This pattern may indicate improved carbohydrate utilization due to RYGB. RQ has also been measured after VSG, but the patterns are less clear. In one study (62), VSG-operated rats demonstrated reduced daytime RQ that is similar to pair-fed an-

imals, but RQ during the nighttime was more similar to the obese, sham-operated animals. Because these data compared three groups with very different eating patterns, these data are hard to interpret and even more difficult to compare to fasting-and-refeeding studies performed in RYGB-operated animals. Future studies should explore the effect of VSG on RQ during fasting and refeeding and, better yet, should provide a head-to-head comparison of these changes after RYGB *vs.* VSG.

V. The Role of Gut Hormones and Other Peripheral Players

A. Leptin and leptin sensitivity

An important reason why individuals fail to maintain significant weight loss induced by lifestyle modifications (diet and exercise) is that negative energy balance elicits potent regulatory responses. These responses include increased hunger, decreased satiety, and decreased energy expenditure (128). Reduction in plasma leptin levels is the key event that initiates these responses by altering a number of key regulatory circuits within the CNS. Consistent with the large reduction in fat mass, plasma leptin levels do drop after RYGB, VSG, and AGB (40, 46, 57, 58, 62, 129–131). Interestingly, the reduction in plasma leptin levels after RYGB exceeds the reduction observed in weight-matched control subjects (46). This enhanced reduction in leptin after weight loss has also been observed in VSG-operated rats as compared with pair-fed rats of equivalent body weight (62).

After VSG and RYGB, humans exhibit a similar rate of change in plasma leptin levels (130). This reduction is significant for both RYGB- and VSG-operated patients only 1 wk postoperatively, before the majority of their weight loss. These data, along with reports documenting less robust decrease to plasma leptin after AGB (46), support the idea that RYGB and VSG share mechanistic properties that are distinct from the physiological changes elicited by AGB. For example, because leptin is produced in the gastric fundus (132), exclusion of nutrients from the fundic mucosa might produce more exaggerated reductions in plasma leptin levels than expected for the level of observed weight loss. Because no gastric tissue is actually removed from the path of nutrient flow after AGB, leptin is not expected to follow this trend. Another possibility is that the immediate reduction in plasma leptin might result from changes to adipocyte function after RYGB and VSG, perhaps downstream of rapid improvements to glucose homeostasis.

The key point, however, is that despite the large decrease in circulating leptin, bariatric surgery appears to avoid many of the responses to negative energy balance that serve to make sustained weight loss difficult. Patients after either RYGB or VSG report decreased hunger and increased satiety (133, 134). As discussed above, animal models of bariatric surgeries provide similar answers. After either RYGB or VSG in rats, we did not observe increased lever pressing for food on lean reinforcement schedules as occurs when animals are food restricted (79). Moreover, there is clear evidence of increased satiety in both RYGB and VSG rats. Both show premature termination of meals and increased c-fos in response to nutrients in brainstem areas linked to satiety (A. P. Chambers, H. E. Wilson-Pérez, B. E. Grayson, K. K. Ryan, S. C. Woods, D. A. Sandoval, and R. J. Seeley, unpublished data, 2012). RYGB-operated rats have reduced hedonic responses to high-calorie liquids, favoring formulas of reduced fat or sugar concentration (136). Specific hedonic assays have not yet been applied to VSG animals, but in the case of both RYGB and VSG, it is clear that reduced food intake is not merely a response to physical restriction but instead is due to enhanced response to nutrient loads.

One potential way in which surgery could blunt the responses to decreased leptin would be to increase leptin sensitivity, thereby requiring less leptin to inhibit responses to negative energy balance. Most obese individuals have very high levels of circulating leptin, and exogenous leptin treatment in these individuals produces little or no weight loss (137). Impaired leptin action in obese individuals is termed leptin resistance and is assumed to contribute to the difficulty of most traditional obesity therapies to produce weight loss without hyperphagia. Thus, it is almost axiomatic that bariatric surgeries are effective to reduce body weight in obese individuals who are likely to be leptin resistant. Whether surgery directly impacts leptin action is difficult to assess in humans and has been directly studied only after VSG among bariatric procedures (62). Sensitivity to exogenous leptin is improved after VSG, but this improvement follows the expected level of resensitization secondary to body weight loss. In this study, VSG had no advantage over caloric restriction to improve leptin sensitivity. The study concluded that improved leptin sensitivity must not cause reduced hyperphagic drive and loss of body weight after surgery, because expression of the leptin-responsive genes, *POMC*, *AgRP*, and *NPY*, were unaltered in the mediobasal hypothalamus. Furthermore, VSG is effective in rodent models of obesity where leptin sensitivity cannot be increased due to a lack of functional leptin receptors (68, 139). Our conclusion from these available data is that although RYGB and VSG reduce the normal responses to negative energy balance, they do not rely primarily on increased leptin sensitivity to do so.

B. Ghrelin

Many consider ghrelin the flip side of leptin in the response to negative energy balance. In 1999, the hormone hypothesized to act at the orphaned G protein-coupled GH secretagogue receptor was discovered to be a peptide of 28 amino acids produced in both the stomach and duodenum (140) and pancreas (141). The hormone stimulated the release of GH *in vitro* and *in vivo* and was termed ghrelin from the Proto-Indo-European root of the word grow. The inactive form of the peptide (des-acyl-ghrelin) is converted to the active form of the peptide (acyl-ghrelin) when preproghrelin undergoes a posttranslational modification by the ezyme ghrelin *O*-acyltransferase (GOAT), resulting in the esterfication of a medium-chain fatty acid to a serine 3 residue that is necessary for binding to and activating the GH secretagogue receptor (142). Given exogenously, ghrelin stimulates food intake in rodents (143, 144) and in humans (145).

The reasons to expect that ghrelin might be altered after bariatric surgery are numerous and include a postulated role for ghrelin as a hunger hormone (146). Because VSG involves the removal of ghrelin-producing mucosa, considerable attention has been given to the hypothesized role of reduced ghrelin to mediate weight loss and metabolic improvement after the surgery. Conservative estimates imply that at least two thirds of circulating ghrelin is produced by X/A-like cells of the gastric mucosa (147), and there is considerable evidence that circulating ghrelin levels are reduced after VSG in humans (42, 59, 148, 149) and in rodents (150–152). In contrast, the stomach remains intact in AGB, and although comparatively fewer studies have assessed the effect of this surgery on ghrelin, the general consensus is that ghrelin levels are increased after band surgery in humans (149, 153) and rodents (151). In RYGB, the stomach is partitioned into a small gastric pouch that is physically separated from the greater stomach or what is often referred to as the gastric remnant. Although dozens of studies have attempted to measure ghrelin levels after RYGB, the literature is fraught with controversy and, in many cases, conflicting results (154–156). Such ambiguities have been discussed in numerous reviews (154–156), and suffice it to say there are a number of issues to consider when measuring ghrelin and interpreting results.

Levels of acyl-ghrelin (active) and des-acyl-ghrelin (inactive) levels increase before a meal and fall immediately afterward in rodents (157) and humans (158, 159). Although acyl- and des-acyl-ghrelin circulate in proportion to one another in free-fed conditions, in humans that are fasted, the des-acyl form of the peptide becomes the dominant form (158, 159), increasing significantly over time, whereas levels of acyl-ghrelin sharply decline. In part, this may be related to the fact that specific dietary lipids are needed as the acylation substrate for GOAT (142); however, anticipation and expectation of nutrients can also play a role (157). For the above mentioned reasons, it is important to consider whether acyl- or des-acyl-ghrelin were measured and the conditions under which samples were collected when interpreting data. In particular, the preservation of intact ghrelin requires careful handling with respect to proper pH levels and the inhibition of proteases by temperature, calcium chelators, and protease inhibitors (159, 160). In addition, ghrelin levels are inversely related to fat mass. For this reason, it is important to consider whether or not ghrelin levels increase in a way that is proportionate to the amount of weight loss after surgery or whether surgery alters ghrelin levels independently of adiposity. Most studies indicate that VSG reduces total (acyl plus des-acyl) plasma ghrelin levels, but whether this change provides any mechanistic basis for weight loss and maintenance is uncertain.

As mentioned above, total ghrelin levels are not always indicative of active levels of the peptide, and it is certainly conceivable that increases in the expression of GOAT could increase levels of acyl-ghrelin after VSG to compensate for reductions in the amount of preproghrelin. Consistent with this idea, although most studies report that total ghrelin or desacyl-ghrelin is reduced after VSG, two papers, one published in 2009 (68) and the other in 2011 (161), report that there are no differences between pre- and postoperative levels of acyl-ghrelin after VSG in rats. Similar reports have emerged after RYGB in humans (162), fueling speculation that this peptide has little to do with the metabolic benefits of either surgery. However, in these experiments (68, 161, 163), the samples were collected in a way that would likely fail to preserve, or prevent, acyl-ghrelin from degrading, and nutritional status was not accounted for, potentially making it difficult, if not impossible, to detect differences among groups. Moreover, in both studies, rats were anesthetized during the collection process that may have also impacted the results. To measure the effect of VSG and RYGB on ghrelin levels under different nutritional states, we measured acyl- and des-acyl-ghrelin at different times in rats maintained on a feeding schedule for many weeks. We found that short-term fasting significantly increased acyl- and des-acyl-ghrelin in all groups except for VSG rats. After the animals were re-fed, circulating levels of acyl-ghrelin were similar among treatments. The results indicate the importance of proper collection methods and different nutritional states when measuring ghrelin. Furthermore, these data support the hypothesis that ghrelin could potentially explain the effects of VSG on appetite and weight reduction.

However, it is also possible that reductions in acyl-ghrelin levels are compensated for by increasing expression, or sensitivity, of the GH secretagogue receptor (151) or by changes in other pathways designed to compensate for absence of ghrelin. To assess whether ghrelin plays a role in the metabolic benefits observed after VSG directly, we examined the effect of VSG on animals that lack a functional copy of the ghrelin gene and compared them with wild-type controls. To our surprise, we found that the effect of the surgery on body weight and glucose homeostasis in these animals was unaltered (A. P. Chambers, H. E. Wilson-Pérez, B. E. Grayson, K. K. Ryan, S. C. Woods, D. A. Sandoval, and R. J. Seeley, unpublished data, 2012). Ghrelin-deficient mice lost a similar amount of weight as wild-type mice and showed the same improvement in glucose tolerance during a mixed-meal tolerance test. Ghrelin-deficient mice also displayed a decreased preference for fat, consistent with effect of the surgery in wild-type mice and rats. Taken together, these data imply that despite evidence to the contrary, the surgical ablation of ghrelin is not responsible for the benefits of VSG or RYGB on food intake or body weight.

C. Cholecystokinin (CCK)

CCK is a classic satiety hormone responsible for modulating hunger in response to meal onset. In response to a meal, CCK is released rapidly into the circulation from the duodenum and jejunum (164, 165). Fat- and protein-rich meals are particularly potent stimuli for CCK release (166), but CCK is also released in response to gastric distension (167). CCK suppresses food intake by reducing meal size through its action on CCK receptors on vagal afferents (168). Because meal size is known to be reduced after VSG (62) and RYGB (78) and anecdotal evidence indicates that meals may be smaller after AGB, increasing attention has focused on whether increased CCK secretion and/or action might be related to weight loss after these procedures.

VSG, ABG, and RYGB involve reduction in functional gastric volume. Total gastrectomy, an extreme form of gastric volume reduction, increases CCK release in humans (169, 170) and in rats (171). Increased circulating CCK mediates reduced food intake and weight loss after the procedure, because chronic CCK-A or -B receptor blockade in rats abrogated these effects (172). Additionally, central sensitivity to CCK may also be increased after total gastrectomy, because enhanced postprandial CCK-A receptor-dependent activation of the nucleus of the solitary tract has been demonstrated after total gastrectomy (173). Very few studies have focused on CCK after bariatric procedures, and CCK has not been measured after VSG, but initial studies demonstrate no change to plasma CCK after either RYGB (40, 86) or AGB (174). Furthermore, a recent study has demonstrated that RYGB is effective in CCK-1-deficient, Otsuka Long-Evans Tokushima Fatty (OLETF) rats (175).

D. Glucagon-like peptide-1

GLP-1 is a product of the preproglucagon gene produced by enteroendocrine L cells that line the lumen of the gut. These specialized cells release GLP-1 in a nutrient-dependent manner, resulting in the release of insulin through actions on GLP-1 receptors expressed on β-cells (176). In addition to its incretin effect, GLP-1 inhibits gastric acid secretion (177, 178), gastric emptying (177), glucagon secretion (177, 179), hepatic glucose production (180), and food intake (181) through actions that involve the coordinated effects of GLP-1 receptors expressed in the periphery and CNS.

Over 10 yr ago, increases in postprandial GLP-1 release were hypothesized to drive the weight-independent effects of RYGB on glucose tolerance and the superior resolution of type 2 diabetes (182–184) compared with purely restrictive procedures such as the AGB. However, increases in postprandial GLP-1 levels after RYGB surgery were actually only shown for the first time in 2006 (185). Three years later, Peterli *et al.* (56) showed that VSG produced qualitatively and quantitatively similar increases in postprandial GLP-1 levels as RYGB. The results were surprising, given that similar increases were not observed in other restrictive procedures (185) and the distinct anatomical differences between RYGB and VSG surgery. The reason postprandial GLP-1 and insulin levels are altered in these procedures continues to be investigated.

Since that study, similar increases in GLP-1 release have been repeated in humans (49, 129, 186) and rodents after undergoing VSG (48), but up until recently, the relationship between the increased incretin effect and improvements in blood glucose parameters after VSG and RYGB surgeries has been correlative. Like Peterli *et al.* (56), in our study (48), rodent models of RYGB and VSG produced equivalent increases in postprandial GLP-1 (Fig. 2) and insulin levels and nearly identical improvements in glucose tolerance. These data were the first to establish that the large increase in active GLP-1 after RYGB and VSG are responsible for the increased insulin secretion during a meal and also establishes that the incretin effect is an important weight-loss-independent effect of both surgeries.

Pair feeding is used to control for the effect of caloric restriction on blood glucose parameters. Determining a role for increased postprandial GLP-1 release on food intake and body weight directly after these surgeries will likely prove much more difficult. GLP-1 is a potent anorectic peptide and higher postprandial levels of this hormone could be part of the reason for the superior effects of

Figure 2.

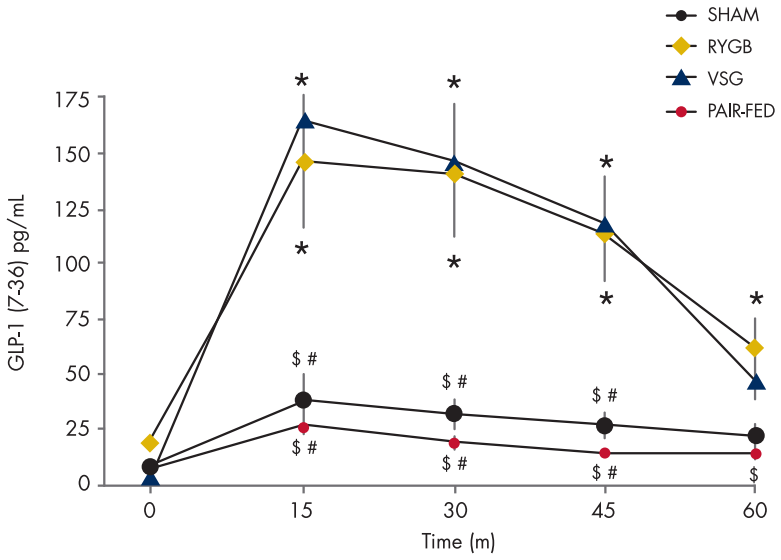


Figure 2. RYGB and VSG are associated with comparable postprandial GLP-1 secretion. *, $P < 0.05$ *vs.* pair-fed; #, $P < 0.05$ *vs.* VSG; $, $P < 0.05$ *vs.* RYGB. [Data from Chambers AP *et al.*: Weight-independent changes in blood glucose homeostasis after gastric bypass or vertical sleeve gastrectomy in rats. *Gastroenterology* 141:950, 2011 (48), with permission. © Elsevier.]

RYGB and VSG on satiety, relative to the effect seen after AGB. However, unlike glucose tolerance, which can be studied acutely, pharmacological interventions designed to test the hypothesis that GLP-1 mediates part or all of VSG's or RYGB's effect on body weight will have to contend with issues related to long-term pharmacotherapy such as tachyphylaxis. This may be one reason why chronic treatment with a GLP-1 receptor agonist does not produce the same degree of weight loss or improve blood glucose as much as either VSG or RYGB surgery (187). Specific populations of GLP-1 receptors have divergent effects that can also limit their pharmacological manipulation; route of drug administration might preferentially target one population over another. One way to overcome this obstacle is to assess these surgeries in mice that lack a functional copy of the GLP-1 receptor in a tissue-specific manner to delineate the different metabolic benefits produced by these surgeries. Other than the established role of GLP-1 in the incretin effect, the fundamental role of GLP-1 release on food intake, body weight, insulin sensitivity, taste preference, and other effects of VSG and RYGB remain to be tested.

E. Peptide YY

PYY is a hormone that, like GLP-1, is released from ileal L cells in response to luminal nutrients. Thus, PYY secretion may be expected to parallel changes in GLP-1 release in bariatric surgery patients. PYY has numerous roles in the GI tract, to increase ileal fluid and electrolyte absorption, inhibit pancreatic and gastric secretions, attenuate gallbladder contraction, and slow gastric emptying (188). Either ip injection (of either $PYY_{1–36}$ or PYY_{3-36}) (189, 190) or intraarcuate injection (of PYY_{3-36}) (189) of PYY has been reported to reduce food intake, although considerable controversy remains about whether this is a physiological role of PYY (191–193). RYGB is associated with exaggerated postprandial PYY secretion (46, 56–59). This effect increases over time after surgery (194) and is present as early as 1 wk after surgery (56). PYY has been reported to be integral to RYGB-induced weight loss, because short-term weight loss is attenuated in mice that do not make PYY (195). Furthermore, weight regain after RYGB in humans has been linked to low plasma PYY levels (196).

Perhaps consistent with a lack of intestinal diversion with banding, AGB does not elicit changes to postprandial PYY levels (46). Surprisingly, however, this is not the case for VSG. Postprandial PYY levels are potently increased after VSG, a response that is comparable to that which is observed after RYGB (56, 59). The basis for an intestinal response after VSG remains unresolved but is likely related to the same mechanisms that drive increased GLP-1 secretion. Uncovering these mechanisms is important, because it will lead to the understanding of physiological targets common to both VSG and RYGB. Identification of these targets is critical to the development of novel therapeutics for obesity.

F. Intestinal gluconeogenesis

Data suggesting that intestinal gluconeogenesis is an important mechanism of improved glucose tolerance after bypass procedures has recently emerged (197). In one study, intestinal gluconeogenesis was found to be increased in mice that received a modified bypass surgery in which the proximal bowel was bypassed, and gastric contents were diverted into the distal jejunum via a gastric-jejunal anastomosis (197). These mice had improved glucose homeostasis compared with mice that had gastric banding, and these effects were blocked in glucose transporter 2 knockout mice and also in mice that had portal vein vagal denervation. The authors hypothesized that glucose produced by the intestine via intestinal gluconeogenesis might act on vagal glucose sensors within the por-

tal vein to activated afferent fibers, resulting in improved body weight and glucose homeostasis. Whether or not intestinal gluconeogenesis affects glucose homeostasis after VSG has not been established, and whether the intestine is gluconeogenic has been highly controversial (198). Additional research is needed to clarify the role of the gut in this phenomenon.

G. Bile acids

An intriguing hypothesis relates to postoperative changes in bile acids after VSG and RYGB (199). In addition to emulsifying fat in the lumen, bile acids enter the circulation, where they can activate nuclear transcription factors that regulate genes involved in glucose metabolism in the liver (200) and brain (201, 202). Bile acids can also activate TGR5, a G protein-coupled receptor in the gut that has been found to regulate GLP-1 secretion (203). Interestingly, circulating bile acids are increased after both VSG (38) and RYGB (204). Thus, changes in bile acids may also be an important mediator of changes in GLP-1 and glucose homeostasis in these procedures. At present, there are no reports of increased bile acids after AGB.

VI. Ingestive Behavior

Numerous reports show that patients who undergo bariatric procedures decrease their food intake and eat smaller meals after surgery (205–211). This is not surprising considering that RYGB, VSG, and AGB all decrease the size of the stomach or the portion of the stomach that immediately collects the ingested food. What may be less intuitive is that patients often change their food preferences, selecting different foods after surgery and reporting loss of interest or aversion to certain kinds of foods.

An important addition to the literature on this topic has been the investigation of food choice in animal models of bariatric surgery, which corroborate the human findings. There are relatively few reports on this topic to date, but they indicate two important points. First, although the typical methods of measuring food intake in humans (self-report and food diary) are prone to considerable error (212, 213), the results from human studies are not solely due to bias or reporting errors, because more controlled animal experiments highlight the same trends. Second, changes in food choice are due to more than doctor's orders. Although bariatric patients are given considerable dietary counseling (214, 215), the replication of altered food choice in animal models indicates a physiological mechanism contributing to dietary changes rather than simply being a result of compliance with postoperative instructions.

A. Food choice

Energy can be obtained from food in the form of carbohydrate, protein, or fat. Most food sources contain a mixture of these three macronutrients and, in addition, contain a variety of micronutrients in the form of vitamins and minerals. To examine food choice, foods are often broken down into categories (meats, grains, fruits, vegetables, *etc.*) and/or may be analyzed by their macronutrient content. Although there is considerable literature describing altered food choice or food preferences after bariatric surgery, the methodology and categorization of foods varies widely from study to study, making it difficult to draw direct comparisons between them. Another caveat to some of the published reports is that although they report changes in intake of certain kinds of foods, they may not report relative intake. For example, a morbidly obese patient may eat 3000 kcal of food per day before surgery and 1500 kcal after (216). Although this person may decrease their intake of sweets, for example, it may be that the relative intake of sweets (normalized to total caloric intake) is unchanged. Therefore, in the context of decreased caloric intake, increases in intake of a certain kind of food are both absolute and relative, whereas decreases may or may not indicate a true shift in diet choice.

The largest number of published works that examine eating behavior after bariatric surgery have examined RYGB surgery specifically, either quantifying postoperative food choices, comparing those with presurgical food choices or a control group, or comparing RYGB to AGB or other kinds of bariatric surgery. Studies that focus on macronutrient content of food have indicated that RYGB patients decrease their relative intake of fat and correspondingly increase intake of carbohydrate (209, 211, 217), whereas others have shown no difference in the percentage of fat intake compared with the preoperative condition (205), or the trend did not reach significance (216). Thomas and Marcus (218) reported that RYGB patients select low-fat foods at a higher frequency than high-fat foods but, paradoxically, that low-fat foods are more associated with food intolerance. Studies that grouped foods according to other categories have variously reported decreased intake of meat (219), sweets and soda (216, 220, 221), and milk and ice cream (216, 221) and increased intake of fruits and vegetables (209, 221), milk products (209) and poultry, fish, and eggs (209, 220). It should be noted that Kenler *et al.* (216) and Olbers *et al.* (221) found a decrease in the milk and ice cream category, whereas Trostler *et al.* (209) found an increase in milk products, but this difference may be related to both the categorization of foods or that, in the Trostler study, food preferences for RYGB and VBG were averaged together, al-

though they were reported to be similar between the operations.

Animal studies, which measure food intake in a more controlled setting and without the social changes that accompany large amounts of weight loss, support that RYGB causes a decrease in fat intake, with RYGB rats decreasing their preference for a high-fat diet when given a choice between two or more food sources (78, 79, 222). Furthermore, in a two-bottle choice test, RYGB-operated animals show a decreased preference for Intralipid, a fat solution, when compared with sham-operated controls (223).

Fewer published reports examine food choice after AGB, although reports on nonadjustable gastric banding (GB), horizontal gastroplasty (HG), and VBG, which cause restriction of the stomach similar to AGB, may be useful for supplementing the knowledge base on this procedure. In a large survey study, Ernst *et al.* (220) found that, compared with obese controls, GB patients ate more poultry and fish and less pasta, fruit, and bread. Compared with RYGB, band patients consumed less fruit, eggs, and diet soft drinks but more chocolate. Two other studies indicated reduced eating of sweets (224) and cravings for sweets (225) after AGB, although none of these studies normalized the reported changes to total caloric intake.

Several studies have compared the food choices of patients who received VBG or HG with RYGB. Regarding relative macronutrient intake, VBG was reported to decrease fat intake (211), whereas HG was not (216). However, when each of these surgeries is compared with RYGB, the reduction in milk and ice cream and sweets and soda was not as great in either VBG or HG as in RYGB (211, 216). Accordingly, another study found that VBG patients ate more desserts, cakes and cookies, and candies but fewer fruits and vegetables than RYGB patients (221). This same study analyzed macronutrient content and found that VBG patients ate more fat and less carbohydrate than RYGB. Finally, Shai *et al.* (226) report that VBG causes decreased intake of carbohydrates and fats (not normalized to total caloric intake), and those patients eat fewer fruits, vegetables, and sweets and increase their intake of milk, yogurt, cheese, and diet soda.

One limitation of using macronutrient intake to represent food selection patterns, particularly in band patients, is what may be a dissociation between nonsweet carbohydrates such as bread, which are reduced relative to the unoperated condition (220, 221, 226) and relative to RYGB (220, 221), and sweets, for which the results are more variable. Therefore, differing effects of gastric banding on sweet *vs.* nonsweet carbohydrates may obscure the relevance of a macronutrient intake analysis.

No reports of food choice in human patients after VSG were found, although one report indicated that VSG patients decreased their cravings for sweets (225). However, VSG-operated rats decrease their fat intake by approximately 50% compared with sham-operated controls and decrease their preference for a high-fat diet compared with a low-fat diet. Furthermore, this change in food choice is comparable to diet changes in RYGB-operated rats (79).

Taken together, these studies indicate that RYGB is more effective to decrease fat intake than VBG, GB, or HG. Furthermore, RYGB appears to promote the intake of fruits and vegetables, whereas GB, VBG, and HG do not. Both types of surgery seem to decrease the intake of sweets and fatty sweets, although it is unclear whether this decrease is simply proportional to the decrease in total caloric intake or whether it reflects a true shift in dietary preference. VSG causes a decrease in fat intake in a rat model that is comparable to the effect of RYGB, but additional experiments will be necessary to evaluate the effect of VSG on other kinds of foods and in human patients.

B. Food intolerance

One explanation for altered food choices after bariatric procedures is the presence of aversive symptoms after the consumption of certain kinds of foods, which then drives patients to avoid those foods. Collectively, these aversive symptoms are referred to as food intolerance (or poor food tolerance) but may include several different kinds of postprandial distress, including dumping syndrome and vomiting.

Dumping syndrome is a cluster of symptoms that includes gastrointestinal and vasomotor consequences including nausea, abdominal pain, diarrhea, palpitations, and flushing and that occurs when nutrients reach the small intestine too quickly (227, 228). Dumping syndrome is most commonly associated with RYGB (229, 230), and does not appear to occur after AGB or gastroplasty procedures (230, 231). VSG has been widely believed not to cause dumping syndrome (232–234), although a recent report indicates that when provoked in laboratory conditions, some symptoms may occur in a minority of VSG patients (235). However, these findings should be interpreted with caution, because other reports of dumping syndrome do not use this provocation method.

Vomiting is the most common food intolerance complaint after AGB (236). AGB patients must eat small meals and avoid the ingestion of liquids while eating solid food to prevent vomiting. These symptoms cause many patients to shift their caloric intake toward liquid sources (237) (which may be nutritionally maladaptive for weight loss) and, in some cases, are sufficiently severe to prompt band removal (238).

Several studies have compared overall food tolerance between bariatric surgeries. Suter *et al.* (239) showed that food tolerance is better in RYGB than AGB in the long term. Whereas RYGB patients experience the poorest food tolerance in the immediate postoperative period, and gradually improve over time, AGB patients show the opposite pattern, with gradually deteriorating food tolerance. However, this report assessed only food tolerance as a whole and did not evaluate reactions to specific foods. Schweiger *et al.* (240) assessed food tolerance for eight categories of food in several bariatric procedures, including RYGB, AGB, and VSG. Overall, AGB patients had the poorest food tolerance, the highest frequency of vomiting, and the lowest satisfaction with their eating ability compared with other surgeries. RYGB and VSG were more favorable in each of these measures and similar to each other. When broken down by food category, AGB had the lowest tolerance in each of the eight food categories compared with other surgeries, with the poorest tolerance for red meat, bread, and pasta. VSG was similar to RYGB or intermediate between RYGB and AGB in every category except red meat, for which it had the highest tolerance compared with the other surgeries. This study did not include a control group and did not assess tolerance for fatty foods. In a comparison of RYGB and VBG, Olbers *et al.* (221) showed that greater than 30% of VBG patients had intolerance for fruits and vegetables, whole meat, and bread, whereas this did not occur in RYGB. Conversely, almost one third of RYGB patients reported intolerance for fat foods, which did not occur in VBG patients.

Animal studies of food intolerance are scarce due to the difficulty of assessing those symptoms in rodents and the fact that rats cannot vomit. However, two studies have used a conditioned taste aversion paradigm to examine whether an intragastric infusion of a fat stimulus causes aversive consequences in RYGB- or VSG-operated rats. One study showed that corn oil caused a modest taste aversion in RYGB-operated rats but not control rats (223), whereas our work found that RYGB caused no such aversion to peanut oil (79). However, we also found that peanut oil does cause an aversion in VSG rats. These studies indicate that food intolerance does occur in rodent models of bariatric surgery but do not indicate the type of discomfort experienced by the animals, and additional experiments will be necessary to determine the responses of different kinds of food across the various bariatric procedures.

C. Taste acuity

Another factor that may influence a patient's food choices after surgery is the ability to detect taste stimuli. Two studies used laboratory taste detection protocols to examine RYGB patients pre- and postoperatively. Both studies found that RYGB patients decreased the detection threshold (increased sensitivity) for certain taste stimuli after surgery. The first reported increased taste acuity for bitter and sour and a trend for salty stimuli (241), whereas the second reported increased acuity for sweet but not bitter (242). Interestingly, another report that used a survey procedure (*i.e.* "Have you experienced a decrease in taste for sweet foods?") found contradictory results. This comparison of RYGB and AGB (which did not include a control group or preoperative evaluation) indicated that 65% of RYGB patients reported a decrease in the taste of sweet foods, whereas 62% of AGB patients reported an increase in the same. Responses for detection of other taste stimuli were more mixed. Overall, more RYGB (82%) than AGB patients (46%) reported a change in the taste of food or beverages after surgery (243). Rat studies of RYGB have also indicated possible changes in taste detection (175, 222, 223, 244), although the procedures used (rapid access lick test and two-bottle choice test) do not distinguish between detection and liking of the stimuli and are discussed in further detail in the next section. No studies of taste acuity in relation to VSG surgery have been reported.

D. Food reward

Finally, bariatric patients may decrease intake of certain foods due to decreased food reward; that is, after surgery, these patients may like or want those foods less. Although this may be a general decrease in food reward related to all caloric sources, it may also vary according to kind of food. And furthermore, these changes may be learned based on experiences with food intolerances or taste acuity.

Using the Power of Food Scale, a questionnaire that measures an individual's hedonic appetite for highly palatable foods but not the actual consumption of such foods, Schultes *et al.* (133) reported that hedonic hunger, the craving for food in the absence of physiological need, is increased in obese individuals, but reversed by RYGB. Furthermore, this measure was most reduced in RYGB patients who reported frequent episodes of dumping syndrome. Similarly, RYGB patients reported decreased thinking of food as well as several other measures of hunger sensations (134). In a comparison of VSG and AGB, more VSG patients indicated a greater loss of hunger and loss of cravings for sweets than AGB patients (225).

Several reports have examined the effects of RYGB on food reward in rat models. One method for examining subjective pleasantness of a taste stimulus is to measure lick rate in a brief access test, with higher lick rates indicating greater liking of that stimulus. However, at low

concentrations, lick rates that are similar to the lick rates for water may indicate one of two things: lack of detection or lack of liking. When rats were examined for their licking response to sucrose, at low concentrations, the results are mixed, with one report (222) showing that RYGB rats have an increased lick rate (enhanced detection/liking) compared with sham controls, whereas two other reports (175, 244) find no differences between groups. However, at higher concentrations of sucrose (well above the threshold for detection), lick rate for sweet tastes is uniformly reported to decrease in RYGB-operated rats (175, 222, 244). In the two studies that examined lick rate for a fat stimulus, Shin *et al.* (222) found increased lick rate in RYGB rats compared with sham rats at low concentrations and decreased lick rate for high concentrations of corn oil. In contrast, le Roux *et al.* (223) found no differences in lick rate for Intralipid at any concentration.

Motivation is another important aspect of food reward, in that patients may eat less due to a decreased drive for food, regardless of how much they like the food once they consume it. Although the Power of Food Scale (mentioned above) is one method for assessing food-related motivation in humans, in rodents, tests that require an animal to complete a task (pressing a lever or simply moving toward a food source) can be used to examine food-related motivation. Shin *et al.* (222) showed that obese rats had a slower runway speed toward a food stimulus (less motivation) than lean rats but that this was reversed by RYGB. These results are surprising because they indicate that RYGB actually increases food-related motivation. Similarly, our group (79) has shown that VSG does not change lever-pressing responses for either a carbohydrate or a fat reward. Contrary to what might be expected, these studies indicate that RYGB- and VSG-operated rats show greater or equal motivation than control rats to work for a food reward, at least in a context in which the total of amount of food consumed is limited. However, when VSG rats were able to lever press for a greater number of food rewards (so that they could presumably reach satiation in the course of the experiment), they lever-pressed fewer times than control rats and consumed less food. Taken together, these studies indicate that intrinsic food motivation is not decreased by RYGB or VSG but that more rapidly achieved satiation decreases motivated responding after the initiation of a meal.

Changes in behavior and perception, such as altered food choice, taste acuity, and food reward, must ultimately stem from changes in the brain. When examined by functional magnetic resonance imaging, RYGB patients exhibited a selective reduction in neuronal responses to high-calorie foods in mesolimbic reward areas (245). Genetically obese rats that received the same procedure exhibited blunted neuronal responses in the parabrachial nucleus to oral sucrose exposure, indicating altered taste processing with RYGB (175). Dopamine, a neurotransmitter associated with various kinds of rewarding stimuli including food, has also been reported to change after RYGB. However, two recent studies offer conflicting reports of the direction of change, with one reporting an increase in dopamine type 2 receptor availaibility (246) and the other reporting a decrease (247).

E. Implications of altered ingestive behavior

The data on food choice and other ingestive behaviors has important implications for understanding the mechanisms of bariatric surgery. In particular, these data strongly refute the gastric volume reduction hypothesis as the primary driver of weight loss, at least in the case of RYGB and VSG. As mentioned earlier, if reduced stomach size caused weight loss only due to a physical limitation on food intake, then we would predict behavioral compensation for that limitation by increasing the ingestion of calorically dense (fat-rich) foods. In fact, VSG and RYGB both cause decreased fat intake. Furthermore, this altered food choice does not appear to be a consequence of food intolerance, because food choices do not reliably correspond to their postingestive effects. Some RYGB patients report food intolerance in the form of dumping syndrome, but these symptoms tend to be relatively well tolerated and improve over time. Food intolerance is even less common with VSG, but the effects on food choice are similar to RYGB.

Importantly, however, the ingestive effects of AGB do not exhibit the same pattern. AGB patients select more fatty foods than RYGB or VSG patients and fewer fruits and vegetables. They are also more likely to consume caloric liquids, which more easily bypass the restricted stomach. In short, there appears to be compensation in the form of behavioral adaptations to circumvent the limitations of the restricted stomach size. Furthermore, many of the alterations in food choice seem to be a direct consequence of food intolerance, particularly vomiting, which can be more persistent and problematic than in RYGB. Overall, AGB patients report the lowest satisfaction with their eating abilities compared with other surgeries, whereas RYGB and VSG receive similarly high marks in this measure.

The open question is the degree to which any of these changes in food choice contribute to the favorable outcomes for these bariatric procedures, particularly in the case of RYGB and VSG, which seem to promote more healthy eating habits. Animal studies provide an intriguing answer to this question. In rodent experiments, the animals encounter a situation that would never be the case

in humans: after surgery, they eat the same high-fat diet that induced their obesity in the first place. Despite this, dramatic weight loss occurs in rodents much as in humans after RYGB and VSG (62, 78). Thus, even when the animal is not allowed to select different or healthier foods, the surgeries exert powerful effects on weight and other physiological factors. Therefore it appears that altered food choice is a side effect of RYGB and VSG surgeries rather than a primary impetus for weight loss and metabolic benefits.

A related question is whether, in the minority of patients who do not lose substantial amounts of weight, it is because they are noncompliant with directions from their surgeon about what foods to avoid. Again, animal experiments answer this question with an unequivocal no. Rodents receive no instructions to follow after the surgery. In the immediate postoperative period, rodents typically are given access only to liquid diets to avoid potential postsurgical complications. However, after that they are on their own. Even in the absence of nutritional counseling, the surgeries result in dramatic weight loss. The key point is that, at least for RYGB and VSG, the failure to comply with nutritional guidelines is likely the result of a failure to engage key biological systems that underlie both the weight loss and the change in ingestive behaviors. It seems unlikely that such failures to alter their ingestive behavior are the primary reason that patients fail to lose weight. After all, the majority of patients seeking weight-reduction surgery have previously received numerous prescriptions to change what and how they eat. There is no reason to believe that such prescriptions are given more convincingly by their surgeon than their primary care doctor or endocrinologist. The reason patients succeed in following such advice after surgery is the direct result of the biological impact of the surgery on key systems that control food behavior.

VII. Clinical Implications

RYGB is one of the most popular and effective bariatric surgeries available, but recent years have seen an increased share of the market going to less complicated surgeries such as VSG and AGB. Although few studies have compared the effectiveness of all three surgeries, in general, RYGB has been found to have greater impact on both weight lost and resolution of metabolic comorbidities compared with AGB (248). In the past couple of years, many clinical studies have been published comparing RYGB with VSG. Many show similar effects on body weight loss (35, 249, 250) and resolution of obesity-associated comorbidities including type 2 diabetes mellitus (35, 249, 250).

Although it is encouraging that a less invasive procedure could be similarly effective to RYGB, conflicting literature exists. A large retrospective case-control study found that although percent excess weight loss and resolution of nondiabetic comorbidities (sleep apnea and hypertension) were similar between RYGB and VSG, they also found that resolution of type 2 diabetes was significantly lower (62 *vs.* 82% of patients) after VSG than RYGB up to 18 months postoperatively (2). Similarly, another recent study found that compared with VSG, RYGB patients have better weight loss 6 and 12 months postoperatively and greater improvements in lipid profiles and glucose response to an oral glucose load together with 93 *vs.* 47% of patients having a resolution of type 2 diabetes mellitus (64). Even if this trend continues to illustrate that VSG is a less efficacious surgery, there are no other pharmaceutical or behavioral treatments available that causes remission of type 2 diabetes mellitus in approximately 47% of a study population (the lowest remission reported from the above studies). Furthermore, VSG is consistently shown to have fewer complications and require less follow-up care than RYGB (26).

It is possible that descrepancies in the literature comparing the efficacy of VSG *vs.* RYGB results from variance within the study population that limits statistical power (as in Ref. 2) or from a need to stratify patients according to body weight class (as in Ref. 64). Lee *et al.* (64) studied poorly controlled type 2 diabetic patients of lower BMI (25–35 kg/m^2) and with functional β-cells. They found that RYGB produced superior weight loss at 6 and 12 months, as compared with VSG. Studies (discussed above) reporting comparable effects of VSG and RYGB, however, examined patients that fell within the standard criteria for bariatric surgery recommendations (BMI >40 or >35 and at least two comorbidities), and most did not report disease duration or β-cell function in their subjects. This brings to light important issues that should be considered not just for study design but for the future of determining who should have surgery and what surgery they should have. One important outcome of understanding the mechanisms associated with these surgeries is that we may be able to discern what characteristics are associated with better success for a given procedure. In this way, we could optimize the success of a given procedure by tailoring the type of surgery to a patient's individual metabolic derangements.

VIII. Conclusions

Despite the increasing popularity of bariatric surgeries, we still lack a clear understanding of the mechanisms for

Figure 3.

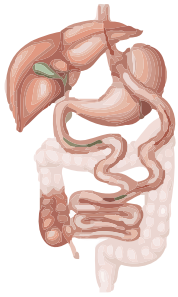
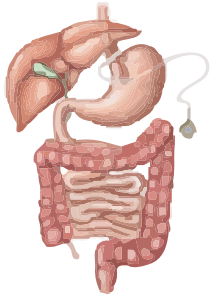
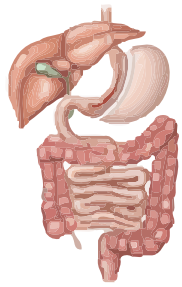
	RYGB	AGB	VSG
			
Lipid homeostasis	Elevated HDL Reduced triglycerides Reduced total cholesterol, LDL	Elevated HDL Reduction in triglycerides not as dramatic as RYGB or VSG	Elevated HDL Reduced triglycerides
Glucose homeostasis	Improved fasting blood glucose and insulin sensitivity, prior to weight loss	Improvements are slower and not as dramatic as after VSG or RYGB	Improved fasting blood glucose and insulin sensitivity, prior to weight loss
Role of gastric restriction	Has not yet been directly tested	Failure of band leads to less gastric restriction and less weight loss	Gastric restriction is not the critical factor preventing hyperphagia
Gastric emptying	Few published studies	No overall change in gastric emptying rate; Emptying rate of proximal pouch created by band is enhanced	Most papers show increase
Energy expenditure	Controversial	Not reported	Unchanged, but only reported in one study
Leptin	Circulating leptin levels lower than expected for body weight Changes to leptin sensitivity not tested	Plasma leptin reduced, as expected for body weight; Changes to leptin sensitivity not tested	Circulating leptin levels lower than expected for body weight; Body weight changes not driven by changes to leptin sensitivity
Ghrelin	Reduced total ghrelin; Controversial, but no change in acyl-ghrelin levels	Increased circulating ghrelin	Reduced total ghrelin; Controversial, but no change in acyl-ghrelin levels
CCK	No change	No change	Not measured
GLP-1 (postprandial)	Weight loss-independent postprandial increase	Increased circulating GLP-1 but much less than RYGB or VSG	Weight loss-independent increase comparable to RYGB
PYY (postprandial)	Increased postprandial PYY levels; Reduced body weight loss in PYY knockout mice	No change	Increased postprandial PYY levels, comparable to levels after RYGB
Bile acids	Increased plasma bile acids	Not reported	Increased plasma bile acids
Diet Change	Decreased fat intake, more fruits and vegetables	Decrease bread intake and increase in caloric liquids; Greater fat intake and fewer fruits/ vegetables than RYGB	Decreased fat intake, similar to RYGB
Food Intolerance	Some dumping syndrome, usually well-tolerated	More persistent and problematic than RYGB; Mainly vomiting	Little or none

Figure 3. Comparison of RYGB, AGB, and VSG.

their success. However, there are a few conclusions that can be drawn from a careful review of the existing human and animal data. First, neither RYGB nor VSG can be thought of as primarily restrictive procedures. Rather, changes in behavior and physiology indicate that both surgeries alter the defended level of body weight, preventing normal responses to food restriction that make maintaining significant nonsurgically induced weight loss so difficult. AGB appears to be different. Many of the behavioral changes and the much less dramatic changes in gut hormone secretion indicate that physical restriction may play a much more important role to produce effects of AGB.

Second, both RYGB and VSG are associated with metabolic improvements that are distinct from those that are caused by weight loss alone. Controversy remains about

this point (see Ref. 135), but our opinion is that in both procedures, the bulk of the evidence from human and animal studies point to important mechanisms that improve a wide range of metabolic endpoints beyond what would occur with weight loss alone and provide an important rationale for both the use and study of these procedures. Again, it appears that AGB is different and that the bulk of its metabolic effects are due to the positive impact of the resulting weight loss.

The important point here is that although many times AGB and VSG are grouped together as purely restrictive procedures that manipulate only the stomach, VSG has physiological effects that are more similar to RYGB (Fig. 3). This is despite the fact that the two procedures are surgically quite distinct with only RYGB changing the route of nutrients through the GI tract and bypassing portions of the small intestine. Our strong belief is that to advance our understanding of these procedures, it is necessary to group them not on the basis of their surgical similarity, but instead we need to group procedures that have similar effects on key physiological variables. In this manner, the strikingly similar effects on key metabolic parameters, ingestive behavior, and gut hormone secretion between RYGB and VSG open up the possibility that they share at least some key underlying mechanisms.

This has an important implication in our understanding of how bariatric surgery works. It has been common to lump mechanistic possibilities for RYGB into either the foregut hypothesis or hindgut hypothesis (202). The foregut hypothesis posits that key improvements after RYGB come from the bypassing of the upper small intestine that results in the reduction of nutrient-dependent actions that would normally impair glucose tolerance (40). The hindgut hypothesis alternatively posits that the key events are the result of more rapid and robust nutrient activation of the distal small intestine such as the ileal brake and increased GLP-1/PYY secretion (138). The common actions of VSG and RYGB directly challenge this distinction because VSG neither bypasses the foregut nor introduces nutrients further down the intestine. Our opinion is that the foregut *vs.* hindgut frame of reference has hindered the field's ability to identify key underlying mechanisms by which these procedures exert their effects. Instead, it is crucial that we identify processes that can link VSG and RYGB procedures (and potentially separate AGB).

Needless to say, the stakes for making progress are high. The opportunity to use these insights to drive more effective and less invasive treatments for obese patients is one that requires more scientific attention from a broader range of fields. We can no longer think of this as just a surgical research problem. With the advent of robust rodent models for these procedures that share both metabolic and hormonal similarities to their human counterparts, endocrinologists and basic researchers have the potential to alter the treatment of obesity and its comorbidities.

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