

Potential mechanisms mediating sustained weight loss following Roux-en-Y gastric bypass and Sleeve Gastrectomy

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Key Points

1. Reduced energy intake, as a result of altered eating behavior, is the main driver for weight loss in humans following RYGB and SG.
2. The biological mediators underlying altered eating behavior post-surgery remain incompletely understood but changed gut-derived signals as a consequence of altered nutrient and/or biliary flow are key candidates.
3. Understanding the interplay between gut hormones, bile acids and the microbiome and their relative roles will enable the development of non-surgical treatment options for obesity.

Synopsis

Bariatric surgery is the only effective treatment for severe obesity. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), the most commonly performed procedures, lead to sustained weight loss, improvements in obesity-related co-morbidities and reduced mortality. In humans the main driver for weight loss following RYGB and SG is reduced energy intake. Reduced appetite, changes in subjective taste and food preference and altered neural response to food cues are thought to drive altered eating behavior. The biological mediators underlying these changes remain incompletely understood but changes in gut-derived signals, as a consequence of altered nutrient and/or biliary flow, are key candidates.

Introduction

Bariatric surgery is currently the only effective treatment for severe obesity, which is defined by a body mass index (BMI) equal to or greater than 40 kg/m², or greater than 35 kg/m² in the presence of obesity-related complications (1). Bariatric surgery involves surgical manipulation of the gastrointestinal (GI) tract, which alters nutrient flow and impacts upon GI biology. These changes engender beneficial effects upon energy and glucose homeostasis (2-4).

Gaining an understanding of the mechanisms underlying the sustained weight loss and metabolic benefits produced by bariatric surgery may hold the key to developing novel non-surgical treatments for obesity and type 2 diabetes (T2D). In particular, it is now clear that altered eating behavior plays a key role in mediating the weight loss following SG and RYGB in humans (5, 6). This has led to intense research efforts focused on delineating how SG and RYGB impact upon the drive to eat.

Historical perspectives

The concept of bariatric surgery emerged in the 1950s from the observation that small intestine resection resulted in weight loss (7). The first procedure aimed specifically at inducing weight loss, a jejunioileal bypass (JIB), where the majority of the small intestine was bypassed, was performed in 1953 (8). The theoretical basis driving the development of the JIB was that weight loss would be achieved through malabsorption. This indeed was the case, however weight loss was coupled with electrolyte imbalances, nutritional deficiencies, diarrhea and liver failure, necessitating the development of less malabsorptive surgical procedures (8). In addition, patients with peptic ulcer disease who underwent gastric resection and/or bypass were also observed to lose weight. In these patients reduced stomach capacity (restriction) and decreased digestion were suggested to drive weight loss (8). This led Mason *et al.* to perform the first gastric bypass procedure for weight loss in 1967 (8). These two different approaches formed the basis for subsequent “malabsorptive” and “restrictive” procedures or “hybrid” procedures, combining these two mechanisms, for example the RYGB, that have evolved over the ensuing 60 years (7, 8). However, it is now recognized that the majority of bariatric procedures engender weight loss and metabolic improvements by mechanisms other than restriction and/or malabsorption.

Over the last decade the beneficial effects of bariatric surgery upon weight and obesity-associated co-morbidities have resulted in a marked increase in the number of bariatric procedures undertaken with approximately 460,000 operations performed in 2013 (9). The choice of surgical procedure has, and still is, evolving guided by technical advances, the beneficial clinical outcomes achieved, short and long-term complication rates as well as by the evidence regarding the physiology underpinning their success. Currently, the most common procedures undertaken globally are RYGB, SG, adjustable gastric banding (ABG) and biliopancreatic duodenal switch (9). Purely restrictive procedures such as AGB and vertical banded gastroplasty are now less commonly performed. RYGB and SG represent the vast majority of procedures undertaken and will form the focus of this review.

Figure 1 near here

RYGB

In RYGB, a small gastric pouch of approximately 20mls is created through dividing the stomach. This is anastomosed with the mid-jejunum, creating the Roux limb, allowing ingested nutrients to bypass the majority of the stomach, duodenum and proximal jejunum (10). Anastomosis of the biliopancreatic limb with the jejunum allows drainage of bile acids and pancreatic secretions, which mix with the ingested nutrients in the jejunum (10). RYGB is established as an efficient treatment for severe obesity, with the long-term (>20 years) outcome data demonstrating sustained weight loss and favorable metabolic outcomes, particularly relating to T2D (11, 12).

SG

SG, intended as a purely restrictive procedure, was initially performed as a first-stage procedure to reduce weight in patients with BMI > 50 kg/m². Following weight loss, this was then transformed into a hybrid procedure such as RYGB. However, SG alone resulted in significant sustained weight loss and metabolic benefits, leading to the adoption of SG as a standalone procedure (9, 13, 14). SG involves transection along the greater curvature of the stomach and removing 80-90% of the total stomach volume, including the fundus and body, without intervention to the small intestine (15). Gastric contents pass rapidly into the duodenum.

SG is technically easier than RYGB, associated with fewer complications, peri-operative and nutritional complications and produces similar short-term weight-loss and clinical outcomes compared

to RYGB (13, 16, 17). Consequently the proportion of SG has increased from 0 to 37% from 2003-2013 and is anticipated to become the most common bariatric procedure undertaken (9). Randomized control trials are currently underway, comparing outcomes post-RYBG against SG in severely obese individuals and comparing the efficacy of the two procedures with regards to resolution of T2D (18, 19).

FIGURE 2 near here

Table 1 near here

Body weight regulation and the impact of obesity

The mechanisms regulating body weight are complex and involve neural circuits controlling energy homeostasis as well as reward-related pathways. Regulatory brain centers continually integrate peripheral signals relating to energy stores and nutrient availability to determine feeding behavior (4). Leptin, insulin and gut-derived factors are established as key regulators of energy homeostasis (20). Peripheral long-term signals, providing information regarding availability of energy stores via insulin and leptin secretion in response to adiposity, and short-term signals regarding nutrient and meal-derived energy availability modulate hunger and satiety perception (21).

Gut hormones are secreted from the GI enteroendocrine cells in response to nutrient ingestion and act as autocrine, paracrine and endocrine regulators of energy and glucose homeostasis (4, 22). The anorectic hormone peptide YY3-36 (PYY) and glucagon-like peptide-1 (GLP-1), an incretin hormone, are both secreted in response to nutrient ingestion from enteroendocrine L-cells present throughout the GI tract (5, 22). PYY has potent anorectic effects, with exogenous administration shown to reduce food intake (23). Evidence from experimental imaging and translational studies indicate that PYY mediates its anorectic effects predominantly by acting upon central appetite-regulating circuits and brain regions involved in food reward (24). There is also evidence that circulating GLP-1 has appetite-suppressing effects by modulating neural activity within homeostatic and reward brain centers, in a manner additive to PYY (25). The orexigenic hormone ghrelin, produced by P/D1 cells in oxyntic glands in the gastric fundus, also acts on homeostatic and reward centers involved in appetite regulation to control energy intake (26). Circulating ghrelin levels increase in the fasted state and decrease post-prandially (22, 26). Elevations in ghrelin levels have been shown to enhance the hedonic responses to eating (27).

Bile acids, in addition to their role in lipid metabolism, influence glucose and energy homeostasis, through signaling and nutrient sensing in the hepatoportal circulation (28). Furthermore, bile acids directly affect the intestinal microbiome through local effects on the intestinal milieu (29). The microbiome, which has recently been implicated in the pathophysiology of several disease processes, also contributes toward energy homeostasis (28, 30). A dysbiotic relationship between host and microbiome could contribute to the development of obesity through increasing intestinal permeability and energy absorption (28).

Taste and olfactory signals influence food selection and, consequently, energy intake (31). Interestingly, there is emerging evidence for an interplay between signals of energy homeostasis and taste and smell. Insulin, leptin, GLP-1, PYY and ghrelin have been found in saliva and their cognate receptors identified on taste buds and olfactory neurons (31). It is now also clear that rewarding food-related sensory stimuli can override satiety signals leading to excess energy intake. Chronic excess energy intake leads to deregulation of the homeostatic mechanisms that normally control body weight, which will predispose an obese individual to further weight gain. (27). Physiological changes in obesity include: resistance to the effects of both leptin and insulin, blunted circulating gut hormone responses to nutrient ingestion, with reduced plasma PYY and GLP-1 levels, dysregulation of circulating ghrelin, reduced circulating bile acids levels, altered gut microbiome and decreased vagal signal transmission (32).

Obese individuals perceive foods high in sugar and fat content more pleasurable compared to lean individuals (33). Furthermore, brain imaging studies have shown increased stimulation of central reward pathways in response to eating or food cues in obese compared to normal weight individuals (33-35). Consequently, eating behavior in obesity becomes dissociated from perceptions of satiety and hunger (36).

Why is weight loss maintenance through non-surgical means so difficult?

Weight loss through intentional caloric restriction results in compensatory changes that aim to defend the higher body weight (35). These include decreased energy expenditure, due to reduced lean muscle mass and reduced sympathetic activity (37), reduced circulating leptin, GLP-1 and PYY levels with increased ghrelin levels (35), altered brain neural response to food cues. Moreover, these

changes are sustained in the long term (35). Table 2 compares physiological responses to weight loss though dieting with bariatric surgery.

Table 2 near here

Sustained weight loss following bariatric surgery

In contrast to weight loss though calorie-restricted dieting, bariatric surgery poses an effective treatment for severe obesity with significant weight loss, sustained in the long-term. Data from the Swedish Obese Subjects (SOS) study shows that after 20 years of follow up, patients who received bariatric surgery had achieved a mean body weight reduction of 18% compared to a 1% mean body weight reduction seen in patients who received standard medical treatment through their local health centres. (11). However, it is important to note that the weight loss achieved post-surgery follows a wide and normal distribution and studying the extreme responders may provide key insights into the mechanisms involved (Figure 3) (38).

FIGURE 3 near here

Mechanisms other than restriction and malabsorption are at play

The multi-factorial mechanisms promoting weight loss and improvements in obesity-related comorbidities following RYGB/SG are incompletely understood. However, it is now clear that the beneficial effects of bariatric surgery are not achieved through restriction and malabsorption alone (39, 40). Reduced energy intake, as a result of altered eating behavior, is the main driver for weight loss in humans (5, 22, 41). Here we review the key eating behavior changes that occur following RYGB and SG together with the potential mechanisms by which RYGB and SG impact upon central appetite-regulating circuits.

Eating behavior changes following RYGB and SG

Changes in eating behavior following bariatric surgery were first suggested by Bray et al (42) in 1980, who observed a reduction in food intake following intestinal bypass. They proposed that 'oral' (taste or smell), 'gastrointestinal' (mechanical distension or nutrient composition) and 'post-ingestional' (nutrient or hormonal satiety mediators) factors as possible mediators (42). Following RYGB and SG patients report appetite changes with reduced hunger and increased satiety (43-45). Post-surgery altered subjective taste and smell together with the food aversions are common and are

thought to drive a change in food preferences away from sweet and high-fat foods (6, 46, 47). Moreover, the reward value of food-related stimuli is decreased post-surgery (6, 48). A study using progressive ratio tasks to assess reward values of food pre- and post-RYGB, revealed a significant reduction in the reward value of sweet and high-fat foods after surgery, compared to a control group (49). Studies using functional MRI scanning have shown lower brain-hedonic responses to food following RYGB compared to AGB, associated with lower palatability of high-fat and energy-dense foods (48, 50, 51). Consequently, a change in the way food is perceived is considered a key contributor toward the altered food preference leading to a lower energy intake post-surgery.

Potential mechanisms underlying eating behavior changes post-surgery in humans

Altered eating behavior following RYGB and SG results in a lower energy intake, which is the main driver for weight loss in humans (22, 52). The biological mediators underlying these changes remain incompletely understood but gut-derived signals as a consequence of altered nutrient and/or biliary flow are key candidates. Interestingly, although RYGB and SG differentially alter GI anatomy, they lead to comparable outcomes in terms of weight loss and metabolic benefits (17, 53).

Gut hormones

A landmark publication by Cummings *et al.* in 2002, showed that circulating ghrelin levels rose with calorie-restricted diets but reduced markedly post-RYGB (54). These findings acted as the catalyst for investigating the role of gut hormones as mediators of the beneficial effects of surgery. Subsequently, there has been some controversy regarding post-RYGB circulating ghrelin levels. However, these differences reflect methodological variability in terms of duration post-surgery and sample processing techniques as the active form of ghrelin, acyl-ghrelin is highly labile and requires specific processing in order to accurately measure circulating levels (55, 56). SG, which involves removing the majority of ghrelin-producing cells, leads to sustained and greater reduction in circulating acyl-ghrelin levels than RYGB (53). Both RYGB and SG are associated with marked increase in nutrient-stimulated circulating levels of PYY and GLP-1 (53, 57). These changes occur prior to and independent of weight loss, pointing towards a procedure-related mechanism. Comparative studies suggest that RYGB leads to greater post-meal PYY and GLP-1 levels compared to SG (53).

Cross-sectional studies have shown that patients with poor weight loss exhibit higher subjective hunger, lower subjective satiety, higher ghrelin and lower PYY and GLP-1 compared to patients with good weight loss (58, 59). Furthermore, inhibition of PYY and GLP-1 with somatostatin analogue, octreotide, leads to return of appetite and increased energy intake and weight gain (60).

Gut hormone receptors for PYY, GLP-1 and ghrelin are expressed on taste buds and there is emerging evidence that these hormones modulate taste (61, 62). Given that the post-operative changes in eating behavior and taste perception overlap with the known effects of changes in gut hormones, it is biologically plausible that these changes can be attributed to increased gut hormone secretion and signaling through gut hormones receptors. Favorable gut hormone responses post-surgery, with increased meal-stimulated PYY and GLP-1 levels, combined with lower ghrelin levels, are clearly associated with higher weight loss. However, the causative factor of this effect is not yet established.

RYGB and SG have been undertaken in transgenic rodents in order to provide mechanistic insights into the role of altered gut hormones. Somewhat surprisingly, global GLP-1 receptor knockout mice exhibit similar weight loss and glycemic improvement following SG and RYGB to their wild-type littermates (63, 64). Similarly, global ghrelin knockout mice respond in a similar manner following SG to their wild-type control mice (65). However, PYY knockout mice exhibit reduced early post-operative weight loss and glycemic improvement compared to wild-type mice (4, 65). These observations suggest that weight loss and metabolic improvements are at least partially mediated by post-operative modulation of PYY.

Other gut hormones with effects on feeding behavior have also been studied. Oxyntomodulin, a pro-glucagon derived peptide with parallel actions to GLP-1 and anorectic effects, has been shown to increase post-RYGB (22). The anorexigenic hormone cholecystokinin has been suggested to act synergistically with leptin and amylin, a pancreatic hormone co-secreted with insulin, may also exhibit anorectic effects (20). However, the extent of their role in mediating the effects of post-bariatric surgery has not been established.

Bile acids and microbiome

Both RYGB and SG induce changes in the interaction between ingested nutrients and bile acids. Despite their anatomical differences, they exert similar effects on bile acids, altering both their composition and secretion (29). RYGB and SG both lead to increased bile acid secretion, which has been linked to improved lipid and glucose metabolism (28).

The metabolic effects of bile acids are mediated through signaling via two receptors; the cell surface G protein-coupled receptor 5 (TGR5) and farnesoid X receptor (FXR) (29). TGR5 is expressed on L-cells and activation of the receptor leads to GLP-1 release. Increased TGR5 activation is a proposed mechanism contributing to higher GLP-1 levels following bariatric surgery (28). The FXR pathways have several functions, including regulating bile acid synthesis, secretion, conjugation and regulation of the intestinal microbiome (28, 29, 66, 67). The latter influences energy absorption, through altering intestinal mucosal permeability, and energy expenditure by intracellular thyroid hormone activation via FXR signalling (28, 68). Following RYGB and SG the intestinal microbiome is altered. Moreover, the finding that transplant of feces from RYGB-treated to germ-free mice resulted in significant greater weight loss compared to mice receiving feces from sham-surgery treated mice suggests that the altered microbiome *per se* contributes to weight loss (69). However, significant differences exist between the rodent and the human microbiome, as well as in the physiological processes driving weight loss. Thus, the relationship between post-operative weight loss and bile acids, FXR signaling and intestinal bacteria in humans remains to be clarified.

Enteroplasticity

Enteroplasticity refers to the post-surgical adaptations, including remodeling of the intestinal mucosa, morphological changes and alterations in innervation (29). Increased post-operative nutrient exposure of intestinal L-cells is thought to lead to enhanced secretion of PYY, GLP-1 and oxyntomodulin (28, 29). There is also evidence that L-cells proliferate and exhibit increased nutrient sensitivity, exhibiting higher responsiveness to the exposed nutrient with resulting higher nutrient-stimulated PYY and GLP-1 secretion (29). Neurophysiological studies suggest that vagus nerve signaling also increases post-RYGB (32). These intestinal adaptations may contribute to the sustained metabolic effects of bariatric surgery.

The future: knife-less surgery?

Bariatric surgery is a safe and highly effective treatment for obesity and T2D. Nevertheless, it requires long-term follow-up and monitoring for complications, nutritional deficiencies and development or relapse of T2D. Despite the increasing numbers of procedures performed, there is high geographic variability in accessibility to surgery. In addition, although bariatric surgery is highly effective, at the individual level clinical response is highly variable. Therefore, developing novel therapies that mimic the post-bariatric surgery internal milieu poses an appealing therapeutic aim. Understanding the interplay between gut hormones, bile acids and the microbiome will be key in order to both fully elucidate both the success of bariatric surgery as well as the reasons behind the variability in response. Such findings would enable the development of non-surgical treatment options for obesity, leading to sustainable weight loss and reduction in obesity-related morbidity and mortality.

Figure legends

Figure 1: Left: Number of bariatric procedures performed by published surveys. Right: Numbers of procedures performed worldwide. Adapted from Angrisani *et al* (9)

Figure 2: Illustrations of (A) normal GI tract, (B) RYGB and (C) SG.

(A) Multiple hormones are secreted from the GI tract. Ghrelin is secreted from the P/D1 cells of the gastric fundus, whereas GLP-1 and PYY are secreted from L-cells located predominantly in the ileum and colon. (B) RYGB; nutrients bypass the majority of the stomach and flow directly into the mid-jejunum. Anastomosis of the biliopancreatic limb with the jejunum allows drainage of bile acids into the common limb, where ingested nutrients and bile acids mix. (C) SG; Nutrients pass rapidly from the gastric sleeve into the duodenum with unaltered flow of bile acids. Following RYGB and SG, circulating ghrelin levels are reduced, meal-stimulated PYY and GLP-1 are increased. Bile acid secretion is enhanced and the microbiome is altered. These changes in gut-derived factors are thought to drive reduced appetite and altered food reward value, leading to a decreased energy intake and weight loss.

Figure 3: Histogram illustrating maximal percent weight loss in patients following RYGB and SG.

Adapted from Manning *et al* (38)

Tables

Table 1: Weight loss, type 2 diabetes remission and complications following RYGB and SG

	RYGB	SG
Weight loss (%WL)		
STAMPEDE (3 years)(70)	24.5+/-9.1 %	21.1+/-8.9%
BOLD data 6 months (13)	26.8%	24%
BOLD data 12 months(13)	34.2%	29.5%
Type 2 diabetes remission at 3 years		
STAMPEDE(70)	38%	24%
Complications (BOLD data) (13)		
All complications	10%	6.3% (P<0.001)
Serious complications	2.5%	2.4% (P = 0.736)

The **Surgical TreAtment and Medications Potentially Eradicate Diabetes Efficiently (70)** trial, investigated 3-year weight loss and remission of type 2 diabetes in patients with type 2 diabetes, randomised to medical therapy or medical therapy plus either RYGB or SG (16). The **Bariatric Outcomes Longitudinal Database (BOLD)** compared weight loss and complications following SG and RYGB (13).

Table 2: Comparison of the effects of weight loss due to ‘dieting’ or following bariatric surgery on signals of energy balance and appetite.

	Weight loss through dieting	Weight loss through bariatric surgery
Ghrelin	Levels increase with dieting (35, 54)	Reduction with SG, possible reduction with RYGB in the immediate post-operative period(53)
PYY	Reduced levels (28, 35)	Increased levels (17, 53, 72)
GLP-1	Reduced levels(28, 35)	Increased levels(17, 22, 53)
Leptin	Reduced levels(71)	Reduced levels.(71) Suggestion that leptin sensitivity may improve (20)
Bile acids	Unclear. Blunted bile acid response in obesity with no significant difference following AGB (73)	Increased secretion
Intestinal microbiome	Improvement with weight loss (74)	Altered (‘leaner’) microbiome (29, 74)
Perceived hunger	Increased hunger (35)	Reduced hunger (43)
Perceived satiety	Lower satiety (35)	Increased satiety (6)
Food aversions		Altered food preference (47)
Long-term sustainability	Average 80% weight regain in 5 years (75)	Average weight loss of 25% at 10 and 18% at 20 years post RYGB (3, 11)
Body weight regulation	Homeostatic mechanisms defend higher body weight (35, 75)	Resets body weight ‘set point’ to lower weight (5)

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