Review

MOLECULAR METABOLISM

Regulation of body weight: Lessons learned from bariatric surgery

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ABSTRACT

Background: Bariatric or weight loss surgery is currently the most effective treatment for obesity and metabolic disease. Unlike dieting and pharmacology, its beneficial effects are sustained over decades in most patients, and mortality is among the lowest for major surgery. Because there are not nearly enough surgeons to implement bariatric surgery on a global scale, intensive research efforts have begun to identify its mechanisms of action on a molecular level in order to replace surgery with targeted behavioral or pharmacological treatments. To date, however, there is no consensus as to the critical mechanisms involved.

Scope of review: The purpose of this non-systematic review is to evaluate the existing evidence for specific molecular and inter-organ signaling pathways that play major roles in bariatric surgery-induced weight loss and metabolic benefits, with a focus on Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), in both humans and rodents.

Major conclusions: Gut-brain communication and its brain targets of food intake control and energy balance regulation are complex and redundant. Although the relatively young science of bariatric surgery has generated a number of hypotheses, no clear and unique mechanism has yet emerged. It seems increasingly likely that the broad physiological and behavioral effects produced by bariatric surgery do not involve a single mechanism, but rather multiple signaling pathways. Besides a need to improve and better validate surgeries in animals, advanced techniques, including inducible, tissue-specific knockout models, and the use of humanized physiological traits will be necessary. State-of-the-art genetically-guided neural identification techniques should be used to more selectively manipulate function-specific pathways.

Keywords Gut-brain communication; Neural controls of food intake; Energy balance regulation; Gut hormones; Bile acid signaling; Gut microbiome

1. INTRODUCTION

The prevalence of obesity is at an alarming level globally (WHO fact sheet on obesity, https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight) and no easy cure is in sight. Behavioral changes and pharmacological therapies can be quite effective, and recent insights into mechanisms that sustain behavior change [1], as well as new drugs currently under evaluation [2], are promising (Figure 1). However, drug treatments often have significant side effects and the beneficial effects of drugs last only as long as they are administered. It is certainly not sensible to expect children or adolescents with obesity to take medication for the rest of their lives.

Bariatric surgery is an attractive alternative, as the procedure is fast and relatively simple with low mortality, and substantial weight loss is typically sustained for many years, if not decades. While bariatric surgery clearly benefits adults with severe obesity, there are potential risks of serious complications and side effects, and some patients regain most or all of the lost weight [3–5]. Furthermore, there are not nearly enough bariatric surgeons to implement it on a global scale. Therefore, it is imperative to understand the mechanisms behind the beneficial effects of bariatric surgery, with an eye towards non-operative treatments that recapitulate these beneficial effects. Although great progress has been made during the last 15 years towards this goal, there is no "smoking gun" mechanism and we still do not have a clear picture of "how" and "why" surgery works so well for obesity when other therapies do not.

The purpose of this non-systematic review is to evaluate the existing evidence for specific molecular and inter-organ signaling pathways that play major roles in bariatric surgery-induced weight loss and metabolic benefits. Such mechanistic insights should provide new impulses towards a more comprehensive and integrative view of body weight regulation and hopefully inform the future development of alternative pharmacological and behavioral therapies. We will explore the many facets and aspects of the controls of food intake and regulation of body weight that are primarily centered on gut-brain communication. The review will mainly focus on Roux-en-Y gastric

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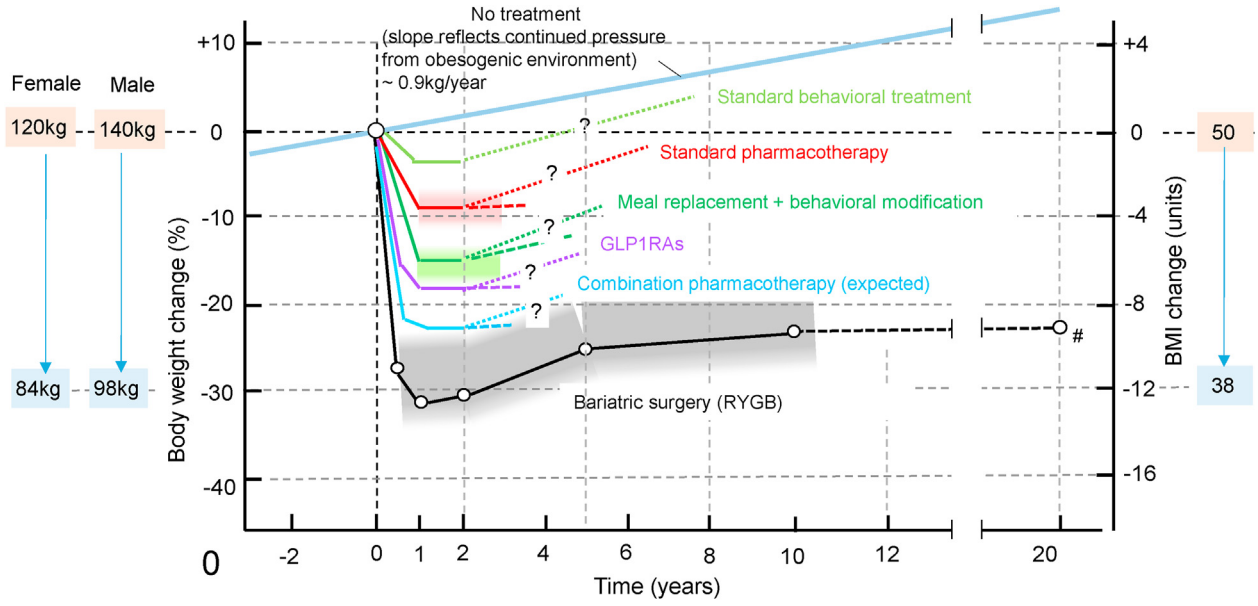

Figure 1: Comparative effectiveness of obesity treatments over time. Expected average changes in body weight and BMI of hypothetical male and female obese patients at age 40 over 20 years either untreated or treated with standard behavioral techniques and lifestyle changes (light green) in combination with standard anti-obesity drugs (red), hypocaloric diets (green), glucagon-like peptide receptor agonists (GLP1RAs, purple), combination pharmacotherapy (blue), or bariatric surgery (black). Based on non-systematically selected, mostly RCT studies. Note that except for bariatric surgery, most studies were limited to less than 3 years follow-up and typically show weight regain after cessation of interventions.

bypass (RYGB) and vertical sleeve gastrectomy (VSG), in both humans and rodents.

2. BARIATRIC SURGERY TYPES AND THEIR EFFECTS ON BODY WEIGHT IN HUMANS AND RODENT MODELS

Among the common bariatric operations, RYGB is most effective in producing a sustained lowering of body weight and adiposity (Table 1). Many, but not all, human studies find VSG to be only slightly less effective [6]. However, mouse models clearly demonstrate the superiority of RYGB over VSG, with VSG mice re-gaining significant amounts of body weight over the first 10 weeks after surgery (the equivalent of about 5 years of human life) [7,8]. In addition, after a nadir at approximately 1 year after surgery, body weight curves in humans with VSG also show a slow but steady trend towards regain [6]. Because the VSG is a relatively newer bariatric operation compared to the RYGB, it remains to be seen what degree of weight regain humans will experience with VSG since mouse VSG models typically demonstrate complete regain of lost weight over time.

One reason for weight regain appears to be the fact that bariatric surgery patients typically remain in the obesogenic environment that is conducive for weight gain in the first place. Given that this environment is the main cause of obesity in a majority of humans, bariatric surgery is only a symptomatic treatment but does not attack the root cause of obesity, which would require removal or neutralization of the obesogenic environment. However, the sustained effects on body weight after bariatric surgery are nothing but remarkable, considering that similar weight loss induced by dieting provokes very strong adaptive and counter-regulatory responses such as increased hunger and reduced metabolism [9,10]. Such counter-regulatory responses are by and large absent in bariatric surgery patients. These patients are simply not as hungry as before, are satiated by much less than prior to surgery, and eat less [11–13], and there is evidence from rodent models that the expected hypo-metabolic response is abrogated [7,14]. It could thus be said that bariatric surgery makes it easier for patients to cope with the hostile obesogenic environment. As indicated by the large variability in weight loss (e.g. for RYGB see Figure 2 in [15]), surgery is not effective in every individual. While the reasons for suboptimal outcomes of bariatric surgery are not clear, the degree of weight loss can be influenced by pre-surgical physiology and behavior as well as genetic background of the patient, skills and techniques of the surgeon, intensity of peri-operative coaching, and the post-surgical environment.

3. BARIATRIC SURGERY CHANGES GUT-BRAIN COMMUNICATION

Gut-brain communication (or the gut-brain axis) is increasingly implicated not only in functional gastrointestinal disorders [16], but also in obesity and metabolic diseases [17,18], and a number of neuropsychiatric disorders (for recent reviews see: [19–21]). Besides absorbed nutrients, metabolites, and hormones, signals generated by gut microbes have attracted much of the recent attention to the gut-brain axis. How surgery changes gut-brain communication is poorly described, despite intensive investigation into how differences in calorie intake, nutrient exposure and nutrient absorption are altered by surgery.

Excessive calorie intake has been recognized as the main cause of obesity for decades [22,23], and therefore bariatric surgery was initially conceived by surgeons to both restrict calories consumed and decrease calories absorbed [24–26]. During millions of years in a rather restrictive environment, the mammalian gut has evolved to very efficiently process and absorb nutrients, including a very large absorptive surface. Reducing ingestive and absorptive capacity to offset the modern environment of plenty seemed like a plausible approach.

Table 1 — Percent total weight loss after RYGB or VSG in humans and diet-induced obese rodents. For human studies, only representative RCTs in male and female patients with obesity, lasting at least 5 years, and reporting total percent weight loss are included. Standard deviation or 95% confidence intervals are reported depending on availability. For rodents, only studies in diet-induced (either 45% or 60% high-fat diet exposure for various time periods) obese male rats or mice and lasting at least 8 weeks are included. Percent weight loss at specific time points in rodent studies was extrapolated from published body weight curves and are estimates only. For some rodent studies difference of final body weight after surgery vs sham surgery is indicated in square brackets. Numbers in parentheses depict the number of subjects. Note that in rodent studies, different starting body weights, housing methods (e.g. single housing), immediate postsurgical regimens, and experimental loads (e.g. frequent blood sampling) may have influenced surgery-induced weight loss. Based on average life expectancy, 2 and 10 weeks of rodent life can be considered as the approximate equivalent of 1 and 5 years of human life.

	RYGB			VSG	
Human	1 year	5–12 years		1 year	5–10 years
Schauer et al. [6]	−29.4 ± 8.9 (50) −10.2 BMI	−23.2 ± 9.6 (50) 5 y −8.1 BMI		−25.1 ± 8.5 (50) −8.9 BMI	−18.6 ± 7.5 (50) −6.7 BMI 5 y
Salminen et al. [279]	−30.6 (120)	−26.9 (120) 5 y		−27.3 (120)	−22.9 (120) 5 y
Arterburn et al. [3]	−31.2 (32,208)	−25.5 (32,208) 5 y		−25.2 (29,693)	−18.8 (29,693) 5 y
Arterburn et al. [280]	−28.4 (17,258)	−21.7 (17,258) 5 y		−23.0 (13,900)	−16.0 (13,900) 10 y
Courcoulas et al. [281]	−33.8 [28.3–39.8] (50)	−28.4 [27.6–29.2] (50) 10 y			
Adams et al. [15]		−26.9 [-28.2 to −25.6] (387) 12 y			
Rat	2 weeks	10–20 weeks		2 weeks	10–20 weeks
Stylopoulos et al. [282]	−19.9 (15)	−12.0 (15) 20w [-21.2]	*Stefater* et al. [119]	−19.0 (9)	+19.8 (9) 17w [-9.8]
Zheng et al. [27]	−18.2 (13)	−16.5 (10) 20w [-24.5]	*Alvarez* et al. [283]	−15.0 (13)	±0.0 (12) 10w [-10.0]
Abegg et al. [284]	−20.5 (7)	−10.2 (7) 10w [-34.2]	*Basso* et al. [285]	−14.3 (21)	+18.0 (21) 10w [-1.3]
Thanos et al. [286]	−15.0 (11)	−19.4 (11) 10w [-24.0}	*Mumphrey* et al. [37]	−18.5 (8)	−6.0 (8) 10w [-13.6]
Mouse					
Hatoum et al. [259]	−34.6 (5)	−17.9 (5) 9w [-34.5]	*Ryan* et al. [243]	−26.3 (8)	±0.0 (8) 10w [-11.6]
Uchida et al. [287]	−28.3 (16)	−21.7 (16) 5w [-24.5]	*Ding* et al. [288]	−26.6 (9)	−14.9 (9) 10w [-21.2]
Flynn et al. [289]	−28.0 (7)	−29.0 (7) 8w [-41.3]	*Du* et al. [290]	−24.5 (5)	−10.2 (5) 10w [-20.0]
Stevenson et al. [8]	−24.4 (6)	−25.6 (6) 10w [-41.6]		−21.7 (6)	−15.2 (6) 10w [+5.0]
Hao et al. [7]	−22.5 (9)	−22.5 (9) 10w [-39.8]		−5.0 (9)	+10.5 (9) 10w [-18.3]

After years of intensive research, it is clear that both of these objectives are achieved at least to some extent. Most modern surgery types are restrictive in the sense that large meals are avoided [12,27], malabsorptive, or both [11,28,29]. Biliopancreatic diversion, the most effective operation for weight reduction, produces the greatest degree of malabsorption [30]. In addition, malabsorption of micronutrients such as iron often necessitate lifelong supplementation [31,32]. However, at least for RYGB and VSG, the effects on macronutrient malabsorption are generally small and cannot fully explain the large and sustained weight loss. It is clear that these bariatric operations go far beyond mechanical restriction and malabsorption and likely impinge on normal physiological mechanisms affecting energy intake, expenditure, and metabolic regulation.

Of the approximately 50,000 studies with bariatric surgery as the search term, the overwhelming majority is strictly descriptive, reporting on changes of structure or function of almost every organ and tissue in the body over time after surgery. They span the entire range from molecular changes in the gut itself to changes in brain and behavior. Many of these changes are either non-specific effects of invasive surgery or secondary to the drastic reduction of food intake and body weight and may not reveal potential mechanisms. The more interesting changes are unique to surgery, in that they are not replicated in controls subjected to similar levels of acute hypophagia and chronic weight loss. The fact that some changes appear rapidly (within a few days) after surgery is often taken as evidence that they are not dependent on weight loss, but the hypocaloric state early after surgery greatly improves many metabolic derangements in obesity before significant weight loss occurs (for a more thorough discussion see section 5), and it is therefore important to control for both hyponutrition and weight loss. It is also important to realize that appropriate controls such as sham surgery are not possible in human studies. Even in rodents, true sham surgery controls are not feasible, as they would require careful re-anastomosis of all cuts made, including functional reconnection of cut nerve fibers, an impossible demand. It is also clear that the changes after bariatric surgery are dynamic, with some occurring within a few hours and others becoming obvious much later, and it is therefore important to clearly state the time after surgery when a change occurs.

The key inter-organ pathways and fundamental energy-balance mechanisms likely involved in the beneficial effects of bariatric surgery on body weight and diabetes resolution are shown in Figure 2. As for any other successful obesity-treatment, bariatric surgery must either decrease energy intake and/or increase total energy expenditure (including any energy lost in the stool). For changes in food intake, food choice, and other behaviors, the brain is the final arbitrator, while for changes in energy expenditure all metabolically active tissues and organs are responsible, although the brain may modulate this capacity via endocrine and autonomic outflow. Therefore, understanding how bariatric surgery affects gut-brain communication is likely to hold the key to unravel its mechanisms.

3.1. Changes within the gut

3.1.1. Gut hypertrophy and L-cell hyperplasia

In humans and rats, RYGB leads to hypertrophy of the nutrient perfused limbs (Roux and common) of the small intestine [33–40], with increased thickness and mass of all layers and a concomitant increase in the number of L- and other enteroendocrine cells [34,35,37]. In rats, hypertrophy is observed as soon as 2 weeks after RYGB [34,40], and after 10 months embraces both the mucosa and external muscle layers [38]. Similarly, total gut weight and length are significantly increased 20 weeks after RYGB in male mice [41], and 40 weeks after RYGB in juvenile mice that prevented weight gain on a high-fat diet in both male and female mice [42]. In contrast to RYGB, none of these changes were

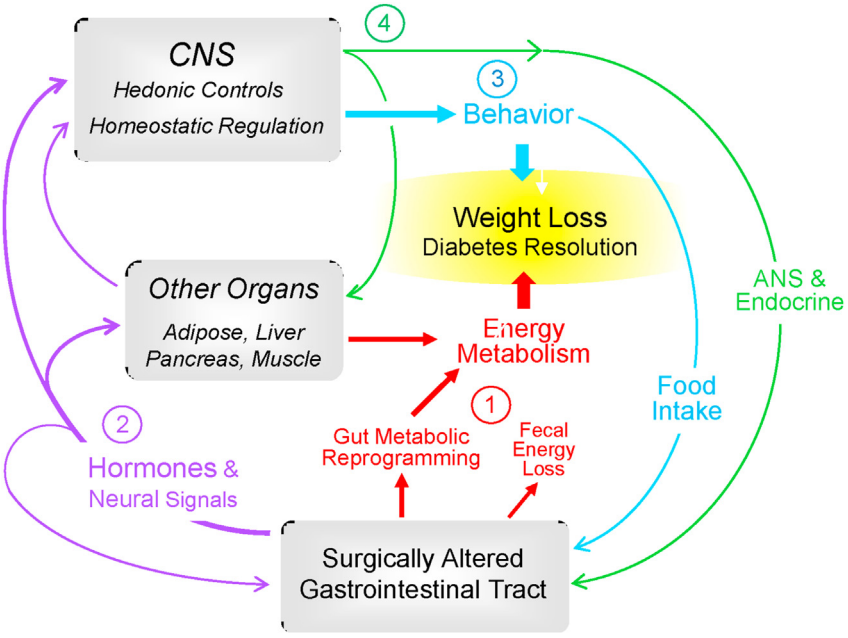

Figure 2: Schematic diagram depicting the principal pathways and mechanisms potentially involved in the effects of bariatric surgery on body weight and diabetes resolution. 1) Changes in energy metabolism and expenditure are determined by fecal energy loss, gut metabolic demands, and energy used by muscle, brown fat, and other tissues. 2) The altered gut generates changes in circulating hormones and other molecules as well as changes in neural signals carried by primary afferent neurons of vagal and dorsal root ganglia origin that affect all other organs including the brain. 3) In turn, the brain orchestrates changes in behavioral output including changes in energy intake and food choice, which affect both energy balance and gut luminal environment. 4) Changes in autonomic and endocrine outflow from the brain can affect all organs including the gut.

observed after VSG in humans and rats [34,37], except for increased numbers of L-cells and increased mRNA expression of GLP-1 [34].

Intestinal adaptation and regrowth are commonly observed after intestinal resection due to Crohn's disease or necrotizing enterocolitis, and considerable efforts have been put into research aimed at finding ways to accelerate regrowth [43–45]. GLP-2, insulin-like growth factor-1 (IGF-1), and epidermal growth factor (EGF) have been found to be part of intestinal growth mechanisms in rodent models of short bowel syndrome (SBS) [46–50] and RYGB [40]. Furthermore, GLP2R-signaling is pivotal for the adaptive response after chemotherapy-induced intestinal injury [51], and long-acting GLP-2 receptor agonists are currently used to treat SBS in humans [52]. However, the critical triggers for intestinal regrowth, such as the key 'ingredients' of the changed luminal contents after bariatric surgery and the respective roles of hormonal and paracrine signaling are not known. It is not surprising that VSG was effective in GLP2R-deficient mice [53], as there is little evidence of gut hypertrophy after VSG. It should be interesting, however, to study the effects of intestine-specific GLP-2 receptor deletion on gut hypertrophy and weight loss following RYGB and whether the different effectiveness between RYGB and VSG can be explained by differential gut hypertrophy.

It is also unclear what factors are responsible for the greatly increased circulating levels of GLP-1, GLP-2, and PYY which are present as early as a few days after both RYGB and VSG; and last for months [33,34,40,54–58]. The increased number of L-cells may be important for RYGB, and increased stimulation may be important after VSG [34].

3.1.2. Metabolic reprogramming

In rats and humans, Roux limb blood glucose uptake is increased after RYGB as measured with 2-deoxyglucose PET imaging [34,39,59], and this increased uptake is associated with increased expression of glucose-transporter-1 (GLUT1) and hexokinase-II (HK-II), the rate-limiting enzyme for glycolysis [39]. Interestingly, this altered GLUT1 not only occurs on the basolateral membrane but the apical membrane as well [34]. This metabolic adaptation or reprogramming appears to be triggered by the sudden exposure to undigested food, as demonstrated by surgically inserting a piece of jejunum between the esophagus and stomach with otherwise unchanged nutrient flow [39], and likely energetically supports the hypertrophic response described above. However, consistent with the absence of a hypertrophic response, there are no adaptive changes in glucose uptake after VSG [34,37]. Furthermore, ex vivo transport of luminal glucose was decreased after VSG [34], suggesting that metabolic reprogramming is different for RYGB and VSG.

Besides glucose metabolism, changes in lipid sensing, transport, and metabolism have also been reported. Twelve weeks after RYGB in high-fat diet-induced obese mice, mRNA expression of several fatty acid sensors in the colon including the GPR40, GPR41, GPR84, and GPR119, known to stimulate GLP-1 release, was selectively increased compared to both sham-operated and calorie-restricted mice [60]. In a rat model of RYGB with a lymph sampling fistula [61], expression of genes in enterocytes implicated in lipid transport and absorption during fasting, and postprandial triglyceride concentrations both in plasma and intestinal lymph were reduced two weeks after surgery [61].

Metabolic reprogramming is not limited to the gut but also occurs in other organs and tissues, as shown in a longitudinal study in rats undergoing RYGB or similar weight loss induced by caloric restriction as a control condition [14]. Notably, the beiging of subcutaneous adipose tissue, increased oxidative metabolism in slow twitch skeletal muscle, and an enhancement of amino acid catabolic processes in the liver occurs in a dynamic fashion and is associated with hypoxia-

inducible factor-1 activation and repression of growth hormone receptor signaling [14].
As pointed out by some investigators, all this reprogramming may potentially explain much of the beneficial effects of bariatric surgery [14,39,60,61]. However, the requirement of any of the hypothesized mechanisms and pathways has not been directly tested in mechanistic studies.

3.1.3. Changes in the gut microbiome

There is an enormous interest in the role of gut microbiota in the pathogenesis of obesity and therapeutic modification of the microbiome (for recent critical reviews see [62–64], but randomized interventional studies are rare. The most persuasive studies with fecal matter transplantation (FMT) in subjects with obesity have shown very modest and mixed outcomes [65–68] and the same is true for studies manipulating the gut microbiome with dietary pre, pro, and synbiotics [69–73].
Not surprisingly, bariatric surgery changes the gut microbiome [74–82]. In a direct comparison of weight loss induced by RYGB vs caloric restriction, the gut microbiome changes were much greater in persons in the surgery group [82]. The more interesting question is whether this change is to any degree causal in the beneficial effects of bariatric surgery [83–86], and the available evidence for a mechanistic role of microbiota is discussed below in section 4.1.3.

3.2. Changes in gut-brain signaling pathways

3.2.1. Circulating factors

As already elaborated above, a number of circulating factors are significantly changed after bariatric surgery. These prominently include the L-cell gut hormones GLP-1, GLP-2, and PYY, which are greatly elevated, but may have limited effects past the liver because of rapid degradation by dipeptidyl peptidase-IV. In addition, serum global metabolomics analyses have identified a great number of metabolites that are changed after bariatric surgery [74,87]. These changes are dynamic [88–90], they vary for different types of surgery [80,91,92], are different for hepatic portal vs. peripheral venous blood [93], are partly independent of weight loss [94], and some of the changed metabolites are associated with the degree of post-surgical metabolic improvements [74,95]. The most prominent among these are changes in the serum bile acid profile and concentrations (see below for a more detailed discussion), lipids, amino acids and their metabolites, microbial metabolites, and circulating markers of inflammation [74,88,89,91]. These circulating molecules have the potential to act in all other organs, including the brain, and contribute to the beneficial effects of bariatric surgery. However, humoral communication is generally non-discrete and relatively slow.
It is important to note that artificially increasing the rate of intestinal nutrient delivery in non-surgical patients can mimic some of these post-operative changes in GLP-1, glucose, and insulin [96]. Even though increased gastric emptying and intestinal nutrient delivery have been posited to explain at least some of the gut peptide effects following bariatric surgery, matched rates of intestinal nutrient delivery show augmented GLP-1 secretion in VSG mice compared to sham [97]. Thus, early and late changes in GLP-1 or other gut peptide secretion may change over time as the intestine adapts, revealing that the timing of measurements in experimental studies is critical. Rates of nutrient delivery may help to explain some of the gut hormonal changes apparent initially after bariatric surgery, though surgery is clearly associated with additional adaptations contributing to altered gut peptide responses that are likely important to driving weight loss and other metabolic effects of surgery.

3.2.2. Sensory and motor neurons of the vagus nerve

The vagus nerve is the principal pathway for discrete and rapid gut-brain communication. It should be noted that both VSG and RYGB operations by themselves are cutting many vagal afferent and efferent fibers (see Figure 4 in [98]. In the case of VSG, this damage is limited to the greater curvature of the stomach. The typical RYGB with a small gastric pouch eliminates most vagal fibers innervating the stomach, and in addition vagal afferent and efferent fibers innervating the pyloric sphincter, proximal duodenum, and parts of the pancreas, as some vagal branches gain access to these targets via stomach and pylorus [99]. However, with normal surgical care, vagal afferents and efferents innervating the distal small intestine and colon, including the Roux-limb, should remain intact in both human and rodent models of RYGB and VSG [98]. Therefore, vagal afferents are in a privileged position to mediate signals emanating from the drastically changed luminal, hormonal, and metabolic environment of the Roux and common limbs. This could be accomplished through the numerous receptors for gut hormones, nutrient metabolites, bile acids, microbial-derived molecules, and other factors [100–103].
High-fat diet-induced obesity has been shown to alter the structure and function of vagal afferents and efferents in rodents resulting in reduced satiety generation and decreased excitability of vagal motor neurons [104–107], it is thus plausible that bariatric surgery may be effective because it reverses some of these impairments. In rats, VSG increased, but RYGB decreased the density of vagal afferent terminals in the nucleus tractus solitarius, and RYGB triggered rapid DNA fragmentation in vagal afferent neurons of the nodose ganglia [108] as well as microglia activation in the dorsal vagal complex [109], indicating neuronal damage. However, RYGB reversed the effects of obesity on the excitability of vagal motor neurons in the dorsal motor nucleus, without normalizing the morphological alterations [104].

3.2.3. Other pathways

Besides communication via vagal afferents, dorsal root afferents via spinal pathways could also play a role in the effects of bariatric surgery but this has not yet been addressed in the literature. Also, humoral communication between the gut and brain could be indirect via crosstalk with other organs (Figure 2).

3.3. Changes in brain function and behavior

We have previously reviewed in great detail the potential recruitment by bariatric surgery of the complex central neural mechanisms responsible for the control of food intake and energy balance regulation in both humans and animal models [110]. Much of the conclusions remain the same, and here we recapitulate a few important points and discuss newer literature.
Data from both humans and rodents show greatly decreased energy intake immediately after surgery, although some of this reduction is typically prescribed by special postsurgical diets. In humans after RYGB, energy intake is still strongly reduced by 20–50% after 2–3 years and by 20% at 10 years [12,13]. In rodents, energy intake returns much more quickly to pre-surgical levels and there is great variability in different studies. In our well-validated rat and mouse models of RYGB with low mortality and complications, energy intake (high-fat diet) returns to near normal 10 days after surgery and remains at that level for up to 10 months in rats [111] and 4 months in mice [112]. However, because up to 20% of ingested energy (mostly fat under high-fat diet conditions) is lost in the feces in both rats [111] and mice [78,113], metabolizable energy intake remains chronically suppressed after RYGB. In addition, rats and mice with RYGB do not exhibit the adaptive hyperphagic response to weight

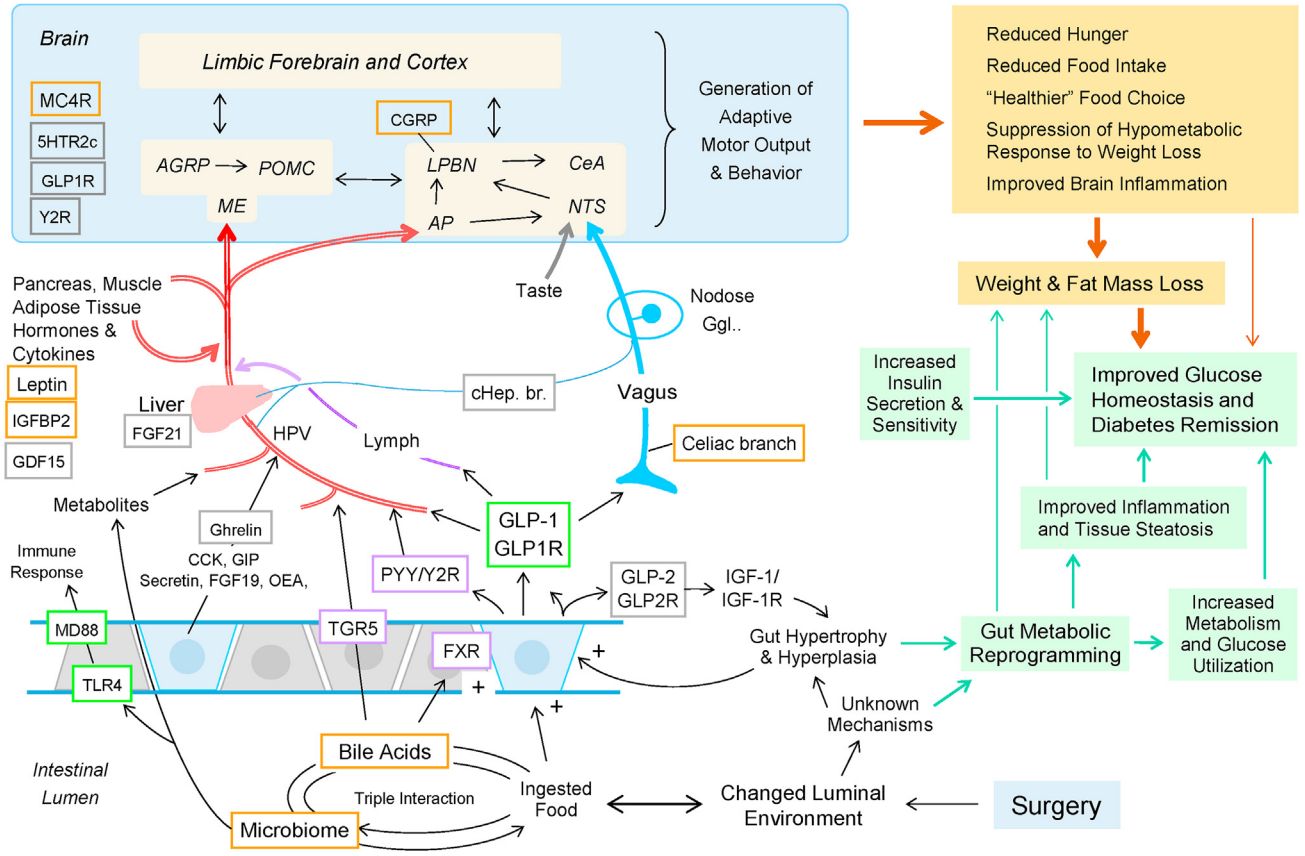

Figure 3: Major candidate signaling mechanisms underlying weight loss-dependent and weight loss-independent beneficial effects of bariatric surgery. Mechanisms affecting body weight through changes in eating behavior and glucose homeostasis through central pathways are shown in yellow-brown. Mechanisms leading to metabolic improvements independent of body weight/adiposity are shown in green. Framing of signaling molecules indicates that their role has been directly tested in transgenic mouse models, or with chronic pharmacological or surgical blockade. Yellow frames indicate evidence for at least partial involvement in effects on food intake and body weight/adiposity with either RYGB or VSG (microbiome, bile acids, leptin/LepR, MC4R, celiac branch of vagus nerve, CGRP neurons in LPBN). Green frames indicate evidence for involvement in improved glucose homeostasis (GLP-1/GLP1R). Purple frames indicate controversial outcomes (TGR5, FXR, PYY/Y2R). Gray frames indicate no effect on outcome of bariatric surgery (Ghrelin, GLP-2, GDF-15, FGF21, brain 5HTR2c, brain GLP1R, brain Y2R, common hepatic branch of vagus nerve). Note that many other hormones besides GLP-1 can activate vagal afferent neurons. Abbreviations, *Brain:* AGRP, Agouti-related protein; AP, area postrema; CeA, central amygdala; LPBN, lateral parabrachial nucleus; ME, median eminence; NTS, nucleus tractus solitarius; POMC, pro-opio-melanocortin. *Periphery:* CCK, cholecystokinin; FGF19, FGF21, fibroblast growth factors 19 and 21; FXR farnesoid nuclear receptor; GDF15, growth and differentiation factor-15; GIP, gastric inhibitory polypeptide; NT, neurotensin; OEA, oleyl-ethanolamide; SCT, secretin; GLP-1, glucagon-like peptide-1; GLP1R, glucagon-like peptide-1 receptor; GLP-2, glucagon-like peptide-2.

loss that is observed after similar weight loss induced by caloric restriction. These observations strongly suggest that the neural circuits responsible for homeostatic energy balance regulation or their inputs are changed after bariatric surgery in both humans and rodents.

3.3.1. Homeostatic energy balance circuitry

AGRP/NPY and POMC/CART neurons in the medial basal hypothalamus are considered a major hub for assessing fuel availability and regulating homeostatic energy balance and body weight [114–116]. Thus, several investigators have asked whether bariatric surgery impinges on this master regulator by measuring mRNA expression of these peptides in rodents. Given its hunger-reducing and satiety-promoting effects, bariatric surgery could be expected to suppress the activity of AGRP/NPY neurons and/or increase the activity of POMC/CART neurons, and this should be reflected in lower mRNA expression for AGRP/NPY and higher expression for POMC/CART. The outcomes were mixed, with changes in both directions [117–120]. However, in a more recent study in which the control mice were body-weight matched through caloric restriction, we demonstrated that mice after RYGB did not show the strong increase in AGRP and NPY mRNA expression seen in controls [121], suggesting that this surgery effectively re-sets the defended body weight on a high-fat diet.

A brainstem circuit including the dorsal vagal complex, lateral parabrachial nucleus, and central nucleus of the amygdala, is intimately linked to the hypothalamus and considered an essential part of the homeostatic regulatory system [122,123] (Figure 3). Activation of this circuit has been demonstrated to strongly suppress food intake [124], and silencing some of its key neurons prevents the food intake-suppressive and satiety-promoting effects of gut-derived and other internal signals such as CCK, GLP-1, GDF15, and intestinal malaise [125–127]. Importantly, this "anorexia pathway" is strongly activated by the new obesity drug semaglutide [128]. The pathway is also strongly activated when a mouse with RYGB, but not a sham-operated mouse, eats food during the early post-surgical period [129]. We also found that silencing this pathway in mice with RYGB results in a transient increase in food intake and a modest reduction of weight loss (unpublished observations). However, GDF15 which also strongly

activates this brainstem anorexia pathway is not necessary for the weight loss induced by VSG [126].

Taken together, these few and disparate observations do not provide a clear picture of how bariatric surgery affects the neural circuits underlying homeostatic body weight regulation. However, striking similarities to the actions of the GLP1R-agonist semaglutide warrant further investigation of the brainstem anorexia pathway and its interface with the hypothalamus and hedonic circuitry.

3.3.2. Hedonic and cognitive mechanisms

Besides a reduction in caloric intake, many clinical studies also report changes in food preferences and food choice, as well as in the 'liking' and 'wanting' of specific nutrients and foods after bariatric surgery [130—137]. Homeostatic mechanisms centering around the hypothalamus have been dominating research in the 20th century, but there is now much interest in the role of hedonic and cognitive brain functions in the controls of food intake and regulation of energy balance [138—140]. The interrelated concepts of food reward [141,142], cue-induced conditioned eating [143,144], executive/inhibitory control [145,146], and their relationship with homeostatic circuits which are mainly controlled by interoceptive signals [147—149], have been in the center of this effort.

Analyses of fMRI studies based on the bold-signal have also evolved - from task-based approaches simply looking at activation or inhibition of specific brain areas to studies assessing connectivity between brain areas and between task-specific networks in the resting state [150,151]. These efforts have identified increased functional connectivity of the orbitofrontal cortex (OFC) and decreased functional connectivity of the insula as the major culprits for problematic eating and obesity [151], and led to formulating the 'triadic model' to explain increased food consumption, consisting of 1) increased sensitivity for, and reactivity to food reward, 2) decreased inhibitory control in executive decision making often combined with increased impulsivity, and 3) numbing of interoceptive homeostatic metabolic signaling [151—154].

Applied to bariatric surgery, most studies demonstrate normalization of impaired activity and/or connectivity patterns in the obese (before surgery) towards patterns observed in lean controls (VSG [155—158], RYGB [155,159—165]). In one study presurgical functional connectivity predicted the magnitude of weight loss induced by VSG [166], and another study found that activation of cortical areas involved in inhibitory control was significantly greater after RYGB compared to VSG [155]. Similarly, in a study looking at sweet taste-related reward and corresponding brain areas, RYGB more effectively reversed the blunted activation in mesolimbic pathways found in patients with obesity compared to VSG [167].

Associations between circulating hormones/metabolites and brain activity/connectivity changes have also been reported in more recent studies with inconsistent outcomes [156,157,165,168—170]. Importantly, a few studies tested the potential role of elevated circulating gut hormones in the effects of RYGB on hedonic and cognitive brain functions by inhibiting either their release or receptor activation [162,163,168]. There was a significant positive correlation between the degree of octreotide-induced plasma PYY suppression (but not GLP-1) and food picture-induced brain reward area activation in RYGB but not in non-obese controls [168]. In ten women with obesity, RYGB reduced food cue-responsiveness of the caudate and reduced activation of the insula to the consumption of palatable food, and blocking endogenous GLP-1 action by infusing the GLP1R-antagonist Exendin 9-39, reversed these (beneficial) effects [162]. Similarly, GLP1R-blockade was found to reverse some of the (beneficial) effects of RYGB on resting state network connectivity thought to be responsible for reducing cue-responsivity and enhancing interoceptive satiety signaling [163].

However, note that systemic infusion of receptor blockers such as octreotide and Exendin 9-39 cannot identify the critical site(s) of inhibition, and that the acute character of these studies does not allow conclusions regarding any longer term effects on food intake and body weight. Furthermore, there are many differences in methodology and the specific brain areas implicated, and one study did not find any significant effects of RYGB or VSG on brain functional connectivity [171].

One significant issue for many of the above studies is the inability to distinguish the direct effects of the surgery from the resulting weight loss. Only one study compared low-calorie diet vs. gastric bypass surgery in order to distinguish between surgery-specific and weight loss-specific effects [161]. In a cohort of mostly female patients with obesity and type-2 diabetes, fMRI scans capturing the response to food cues in the fed versus fasted state were conducted before and 4 weeks after either very low calorie diet (VCLD) or RYGB. Compared to VLCD there was a relative reduction in food cue responsiveness in food reward brain areas, a strengthening of cognitive control regions, and reduced activation in the hypothalamus with increased connectivity to reward areas 4 weeks after RYGB [161]. This may suggest that reduced hunger after RYGB is driving the changes in food reward and that overall RYGB makes it easier to sustain weight loss compared to VLCD.

Effects on food preference and choice are also seen in rodent models after weight loss induced with VSG or RYGB in obese animals [7,27,42,172—176], suggesting differences in brain functions related to taste processing and hedonic and cognitive aspects of food intake. However, changes in taste-guided behaviors such as brief-access licking were not found in an RYGB model that uses lean, chow-fed rats [177,178], suggesting that the prior history of obesity is an important factor in determining behavioral changes after surgery. The potentially underlying neural mechanisms were only investigated in a handful of studies. RYGB in mice increased dopamine turnover in dorsal striatum [179], and RYGB in rats decreases μ-opioid signaling in the central amygdala and hypothalamus independent of diet or caloric restriction [180], and increases GABA-A receptor levels in cortical areas involved in object recognition [181]. In Yucatan mini-pigs exposure to Western-diet resulted in impaired working memory, anxiety-like behaviors, loss of motivation, and snacking-type eating behavior, and although weight loss through caloric restriction reversed most of these aberrant behaviors, RYGB did a better job in normalizing inhibitory control [182]. Finally, Hankir et al. demonstrated that RYGB in rats on a high-fat diet recruited a gut-brain pathway involving intestinal endocannabinoid signaling via oleyl-ethanolamide (OEA), the vagus nerve, and dorsal striatal dopamine receptor-1 (D1R) to reduce fat appetite [183]. However, the relevance of this pathway is not clear, as vagotomy, which abolished the changes in fat appetite, had no effect on RYGB-induced weight loss.

In summary, there is an impressive number of clinical studies demonstrating changes in neural activity patterns after bariatric surgery and their correlation with subjective reports of the patient's attitude towards food items and circulating gut hormones. Most of the findings are consistent with the idea that bariatric surgery reverses the detrimental effects of obesity on hedonic and cognitive controls of eating, making it easier for bariatric surgery patients to reduce calorie intake despite massive weight loss. However, none of the clinical and preclinical studies demonstrates causality for the weight loss and metabolic improvements. Such interventional-type studies will be

difficult to implement in patients, but the use of function-specific neural pathway manipulations in animal models should eventually lead to such mechanistic conclusions.

4. MAJOR CANDIDATE MECHANISMS FOR THE EFFECTS ON BODY WEIGHT

The many changes described in the preceding section could all potentially play a role in the beneficial effects of bariatric surgery. However, few specific hypotheses have been tested with interventional type studies. Of more than 30 studies that directly tested a specific hypothesis by comparing wildtype and knockout mice in their ability to sustain bariatric surgery-induced weight loss, the majority was negative, meaning that there was no evidence for the hypothesized signaling mechanism (ghrelin [184]; GLP-1R [185—187]; GLP-2R [53]; PYY/Y2R [41]; FGF21 [188]; TGR5 [189]; FXR [190]; 5-HTR2c [191]; Clock Delta-19 [192]; NTSR1 [193], GDF15 [126]). Only a handful of studies found at least some consequence of knocking out a specific signaling mechanism on RYGB- or VSG-induced weight loss and or other metabolic improvements (Figure 3). Here we discuss signaling pathways and molecules that have been demonstrated to be at least partially required for the beneficial effects of bariatric surgery in more detail.

4.1. Mechanisms primarily changing food intake

4.1.1. GLP-1, PYY, and their signaling pathways

The first and major hypothesized mechanism involving gut-brain communication is altered gut hormone signaling to the brain, specifically GLP-1 and PYY-signaling. Both GLP-1 and PYY-secretion from intestinal L-cells is significantly and lastingly increased after both RYGB and VSG (but not gastric banding) [54—58,194], and there is a large literature demonstrating the ability of these gut hormones to suppress appetite and food intake in both humans and animals [195—199]. Furthermore, and as outlined in section 3.3.2 above, human neuroimaging studies clearly demonstrate a role for endogenous GLP-1 and perhaps PYY in the beneficial effects of RYGB on the activity of neural networks responsible for the hedonic and homeostatic controls of food intake [162,163,168]. These studies collectively show that endogenous GLP-1 suppresses anticipatory food reward, strengthens cognitive inhibition, and enhances interoceptive satiety signaling in corresponding functional neural networks, and that RYGB with its elevated circulating GLP-1 levels takes advantage of these effects.

Together with the recent success with stable GLP-1 receptor agonists such as liraglutide and semaglutide to produce amounts of weight loss rivaling those of bariatric surgery [2,200—203], it would seem to confirm the long sought-after mechanism. A recent study in rodents with radiolabeled semaglutide and the c-fos neural activity stain highlighted a well-known brain network as likely substrate for the appetite-suppressing and body weight-lowering effects of this stable GLP-1R agonist. This network consists of the NTS and area postrema in the caudal brainstem, and the hypothalamic arcuate nucleus, both converging on the parabrachial nucleus in the pons [128], the main hub of the brainstem anorexia pathway extending from the NTS via the PBN to the CeA and BNST [125]. This circuitry would seem to be in an ideal position to mediate the body weight and metabolic effects of RYGB and VSG via increased GLP-1 signaling.

However, several observations raise questions for such a conclusion. First, studies in rodents with GLP-1 receptor deficiency [185—187] or pharmacological blockade of GLP-1 receptors [187,204] concluded that peripheral and central GLP1 receptor signaling is not required for the beneficial effects of RYGB and VSG on body weight. It should be taken into consideration that these were whole body and germline knockouts, with considerable potential for developmental compensation. Only one study used a β-cell-specific GLP-1R knockout mouse model, and indeed demonstrated that improvement of glucose tolerance after VSG partly depended on GLP-1R signaling in pancreatic β-cells, even though body weight loss was not differentially affected [205]. It remains to be seen whether tissue-specific and inducible knockout models can provide more positive outcomes.

Second, it is not completely clear how GLP-1 of intestinal origin leads to suppression of food intake. Because GLP-1 has a short half-life in the circulation, it is unlikely to reach the brain in high enough concentrations, even with the much higher secretion rate after surgery. Therefore, the prevailing view is that GLP-1 of enteroendocrine origin acts locally on vagal sensory nerve fibers [206—210] or on vagal nerve fibers innervating the hepatic portal vein [211—213] that in turn change activity in brainstem and other brain areas to suppress food intake [207]. The observation that surgical transection of the paired celiac branches of the subdiaphragmatic vagus nerve, partially abrogates RYGB-induced suppression of food intake and body weight in rats [214] is consistent with this idea. By preferentially innervating the small and large intestines [215], including the Roux and common limbs, the celiac branches are in a position to pick up any signaling originating from the rearranged gut. Because surgical transection of the common hepatic branch, which supplies vagal sensory innervation to the hepatic portal vein [216] does not affect the outcome of RYGB in rats [217], it is unlikely that GLP-1 sensing mechanisms within the hepatic portal vein play an important role. Given that these surgical subdiaphragmatic vagal branch cuts included both sensory and motor fibers, the findings are consistent with, but do not unequivocally prove, a role for vagal afferents. So, if surgery-induced elevation of GLP-1 secretion is still considered as part of the mechanism, it would most likely involve vagal afferent mediation to the brain. This is in contrast to how the new stable GLP-1 receptor agonists work [206,207,218]. They seem to primarily activate GLP-1 receptors in the brainstem and hypothalamus and involve the lateral parabrachial anorexia pathway [128,207].

Surgery-induced increased secretion of other anorexigenic gut hormones such as PYY, Neurotensin (NT) and CCK are also plausible mechanisms [193,219]. The acute effects of modified RYGB on body weight were lost in PYY-KO mice [220]. However, global deletion of the PYY/Y2R in mice [41] and brain-specific pharmacological blockade of the PYY/Y2 receptor in rats [187] did not affect the ability of RYGB to reduce food intake, lower body weight, and improve glycemic control. In neurotensin receptor-1 (NTSR1) deficient mice, the ability of VSG to reduce fat preference was reduced, but long-term weight loss was not affected [193].

Failure to demonstrate an effect of knocking out a single pathway could at least partially be explained by the often observed additivity or even synergism between two or more anorexigenic gut hormones. A specific case has been made for the synergistic effects of GLP-1 and PYY on food intake in rodents and humans [219,221,222]. Such synergism is also relevant for the question of developmental compensation following whole-body germline knockouts, as PYY/Y2R-signaling or GLPR1-signaling may take over each other's function in single knockouts. To address this question, we recently generated a GLP1R/Y2R double knockout mouse model [223]. However, RYGB had the same ability to lower body weight and improve other metabolic and glycemic parameters in such double-knockout compared to wild-type mice [223].

In summary, the profound changes in the secretion of gut hormones, in particular GLP-1 and PYY after RYGB and VSG, together with receptors

at all the 'right places', would seem to be in a perfect position to mediate the beneficial effects of these weight-loss operations. However, while there is moderately convincing evidence for an important role of GLP-1 signaling in humans, there is quite strong evidence against it in mice, all be it obtained mostly in whole-body germline knockout models with all their limitations. Therefore, to substantiate a critical role for GLP-1 signaling after RYGB and VSG in humans, future clinical studies could include 1) longer-term administration of GLP-1 receptor blockers, 2) intranasal administration of GLP-1 receptor blockers to distinguish brain-specific from peripheral effects, and 3) direct comparisons of altered brain signaling by bariatric surgery and stable GLP-1 analog treatment. Future preclinical studies with inducible and more selective GLP-1R deletion techniques should also be revealing.

4.1.2. Bile acids and their signaling pathways

Bile acids are synthesized within hepatocytes and are critical for the solubilization and absorption of dietary fat and fat-soluble micronutrients. Once synthesized, conjugated bile acids (taurine or glycine conjugates in rodents and humans, respectively) are secreted into the biliary system and transit to the intestinal tract [224]. Upon reaching the terminal ileum, the majority of bile acids are taken up by high-affinity receptors on the ileocytes, returned to the portal circulation, and then cleared by the liver through high-affinity receptors that creates a highly selective and one-way circulation between the liver and gut referred to as the enterohepatic circulation. (Figure 4). To further increase physiologic complexity, circulating bile acids also increase with intestinal nutrient delivery (i.e. feeding) and peak higher with increasing intestinal lipid delivery [225,226]. Even though only a few primary species are synthesized endogenously [227], bacterial transformation in the intestinal tract and other chemical conjugation (e.g. sulfation, dihydroxylation, deamidation) can lead to numerous bile acid species [228]. These chemical species are the endogenous ligands of several nuclear and transmembrane receptors, most notably the farnesoid X receptor (FXR) and the G-protein Coupled Bile Acid Receptor (GPBAR, TGR5), but also the vitamin D receptor and pregnane X Receptor [229].

Unlike the remarkable effects of stable GLP1R-agonists, clinical trials leveraging the physiological effects of bile acids signaling were little effective for changing food intake and body weight, although they can significantly improve glycemic control in patients with obesity and diabetes [230]. Therefore, the premise for mediating the beneficial effects of bariatric surgery is not as robust for bile acid signaling as it is for GLP-1.

Bariatric surgery is associated with markedly elevated circulating bile acid levels in humans [231–237] and rodents [238]. Fasting and prandial concentrations are augmented by bariatric surgery, and the prandial rise that is lost with obesity is restored by RYGB [231,239,240]. Although many reports demonstrate general increases in bile acids following surgery, studies of the chemical composition require more sophisticated methods and are fewer. Also, whether there are differences in bile acid responses between operations (i.e. VSG and RYGB) remains unknown. Timing is another variable that remains poorly studied, as clinical studies demonstrate increased circulating bile acids as early as 4 weeks postoperatively [232], but data is mixed at earlier time points (~1–4 weeks in humans)

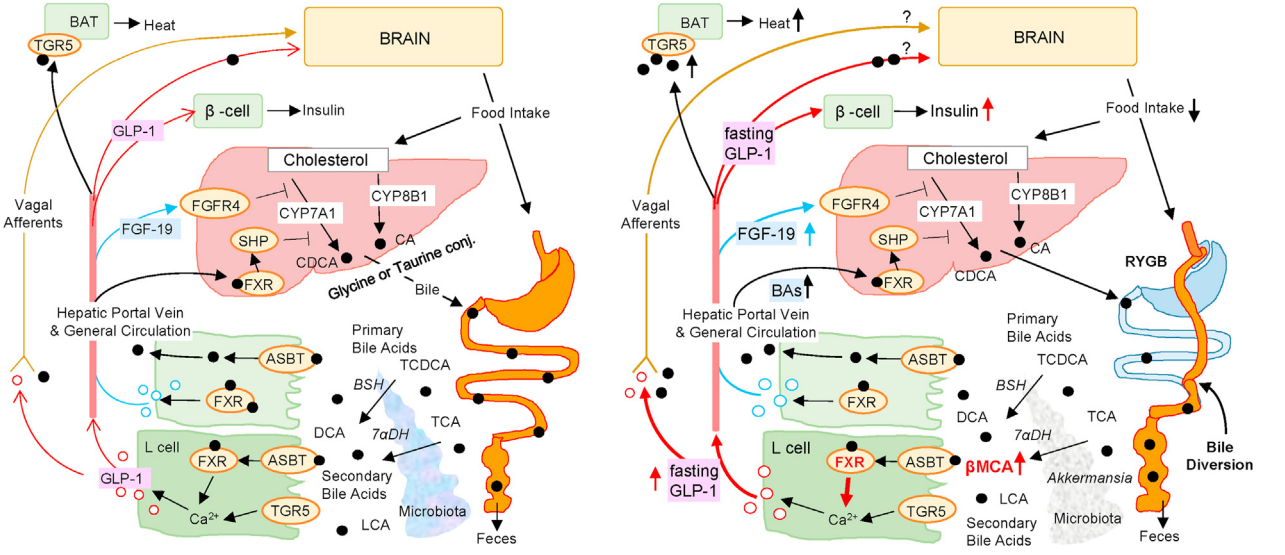

Figure 4: Mechanisms of bile acid metabolism and signaling potentially involved in the effects of bariatric surgery. **Left:** Schematic diagram showing the major components of enterohepatic bile acid homeostasis. After synthesis from cholesterol in the liver and transport via the bile duct and gall bladder to the intestinal lumen, where they are mainly involved in lipid absorption, taurine and glycine-conjugated primary bile acids such as TCA and TCDCA are modified to secondary bile acids such as DCA and LCA by microbiota. Ninety percent of bile acids are then re-absorbed by enterocytes in the distal intestine via the apical sodium bile acid co-transporter (ASBT) and a small fraction is lost in the stool. Re-absorbed bile acids are then transported back to the liver to provide feedback control over bile acid synthesis together with the gut hormone FGF-19/15 which is stimulated via the nuclear farnesoid bile acid receptor (FXR) in enterocytes. Activation of the Takeda G-protein coupled receptor (TGR5) by bile acids stimulates the release of GLP-1 from enteroendocrine cells and activates vagal afferents. From the hepato-portal circulation, bile acids also gain access to the general circulation, where they interact with FXR and TGR5 in other organs and tissues, notably in brown fat tissue to generate heat, and in the brain, where they can affect food intake and autonomic/endocrine outflow. **Right:** After RYGB and following bile diversion to the distal ileum, total bile acids are increased and bile acid composition changes both intraluminal and in the plasma, due to changes in the luminal environment and microbiome. Increased re-uptake of bile acids such as β-muricholic acid (βMA), a potent FXR agonist, leads to increased GLP-1 release and improvement in insulin secretion. Increased bile acid concentrations in the lamina propria lead to increased activation of vagal afferents that suppress food intake. The effects of changes in systemic bile acid signaling after RYGB and bile diversion are not known.

[231,241]. Given that bile acid increases may not be present at these early postoperative time points, when there are clear improvements in glucose regulation, suggests that bile acids may not completely explain the early beneficial effects of RYGB on glucose homeostasis [231,233,234]. This delayed rise in circulating bile acids indicates that a signal stimulating synthesis may be required to drive these increases over time. However, the mechanisms for these dramatic increases in bile acids overall remain unclear. Overall, rodent studies are more limited, but VSG is associated with increased fasting and prandial rises in total bile acids [242] by 2 weeks. Prandial and fasting differences, differences in chemical species, as well as earlier time points post-operatively (earlier than 2 weeks) are poorly characterized to date.

Mechanistic studies have been carried out almost exclusively in mouse models with genetic deletion of either FXR or TGR5. Bile acid signaling through the nuclear receptor FXR was found to be required for the full weight loss induced by either VSG [243] or the diversion of bile to the distal ileum [244], but not for RYGB-induced weight loss [190]. However, RYGB-induced improvements in glucose tolerance and HOMA-IR were partially dependent on a functional FXR [190]. Bile acid signaling through the membrane receptor TGR5, while not required for both RYGB [189] and VSG-induced weight loss [53,245], was partially required for improved VSG-induced glucose tolerance [245]. In other studies using interventional approaches, reduced circulating levels of tauro-deoxy-cholic acid (TUDCA) and valine in high-fat diet-induced obese mice were restored after VSG, and systemic treatment with TUDCA and valine induced the same weight loss as after VSG [246]. Similarly, a specific sulfated cholic acid is enriched in the gut of mice following VSG that is associated with GLP-1 and glycemic control [247]. These interventional studies are beginning to identify how bile acids might modulate post-surgical physiology. Even though bile acids are metabolically active hormones with a plethora of metabolic effects, their specific roles in body weight and other metabolic regulation after bariatric surgery remain unclear. However, recent evidence has demonstrated the importance of TGR5 signaling in the hypothalamus to protect from obesity [248], and in the nucleus accumbens to reduce cocaine reward [249].

In summary, the roles of peripheral and/or central bile acid signaling remains unclear and further studies, especially those using RYGB, require interventional and tissue-specific approaches to clarify how these compounds alter physiology in response to bariatric surgery. The driving force behind the marked increases in bile acid synthesis following bariatric surgery remains unknown, though this mediator could be a potent target for altering metabolic physiology by modifying bile acid levels.

4.1.3. Microbiota and their signaling pathways

As discussed in section 3.1.3, there is no doubt that bariatric surgery leads to profound changes in the gut microbiome. However, the outcome of the few attempts with transplantation of bariatric surgery-modified microbiota to mice is rather disappointing. In one of these studies, transplantation of microbiota from two female RYGB patients after weight loss to germ-free mice very modestly, but significantly, reduced fat mass gain over a two week period compared to transplantation of microbiota from patients with obesity [81]. Transplantation of pooled microbiota obtained from mice with RYGB significantly reduced body weight by about 5% in germ-free mice, but microbiota from sham-operated mice had no effect [78]. Finally, transplantation of gut microbiota from patients with poor weight loss after RYGB into antibiotic-treated recipient mice resulted in significantly greater weight gain compared to mice receiving microbiota from patients with successful weight loss [250]. However, there was no significant difference in weight loss between mice receiving transplants from normal control patients vs. patients with successful weight loss [250].

Potential signaling pathways from gut microbiota to the host may include immune signaling, tryptophan and tyrosine metabolites, as well as bile acids and short-chain fatty acids (for recent review see [251]. For example, transplantation of cecal contents from mice with VSG to germ free mice is sufficient to alter bile acid metabolism and increase the potent TGR5 agonist cholic acid-7-sulfate (CA7S) that is associated with augmented GLP-1 secretion and improved glucose homeostasis [247,252]. Furthermore, deletion of the TLR4-receptor or MYD88 in mice reduced the effects of RYGB on glycemic control. Immune-signaling via TLR4 receptors and myeloid-differentiation factor 88 (MyD88) may be one of the underlying signaling pathways, as deletion of their function resulted in a partial loss of beneficial effects of the surgery on metabolism at 5 weeks after surgery [253]. However, these conclusions are tempered by the fact that the TLR4-KO mouse has a lean phenotype that should make it largely resistant to the body weight-lowering effects of RYGB [253].

In summary, surgery-induced changes in microbiota-signaling may contribute to some small extent to the beneficial effects of bariatric surgery, and individual differences in gut microbiota composition may be predictive of some of the beneficial effects of bariatric surgery.

4.1.4. Other signaling pathways with evidence for a mechanistic role

4.1.4.1. Leptin-signaling. The ability of RYGB to reduce body weight was about 50% less in Ob/Ob mice with leptin receptor deficiency compared to wildtype mice [254]. In another study, RYGB was effective in reducing body weight in obese Ob/Ob mice compared to sham surgery, although at 6 weeks after surgery body weight returned to slightly above presurgical levels [255]. Together, these mouse studies suggest that leptin-signaling is required for the full effects of RYGB on body weight. As plasma leptin levels drop drastically after RYGB [254], which normally triggers increased hunger and reduced metabolism, the ability of RYGB to at least partially suppress these counter-regulatory responses is again demonstrated. Given the wide distribution of leptin receptors, tissue and brain site-specific deletion of leptin receptor signaling will have to be used to ferret out the critical sites of leptin action.

4.1.4.2. Melanocortin-signaling. A recent systematic review of the clinical literature concluded that the MC4R gene is inconsistent in its relationship with the amount of weight loss after bariatric surgery [256]. However, one study demonstrated inferior long-term weight outcome of cases with MC4R variants after VSG compared to RYGB [257], and another study found that MC4R mutation carriers with impaired eating control had more major complications than non-carriers independent of weight loss [258].

Studies in whole body MC4R knockout mice [259,260] as well as a study with long-term pharmacological blockade of the brain MC4R in rats [261] demonstrated the requirement of MC4R-signaling for RYGB-induced weight loss. In the latter study, rats that had lost 15% of body weight after RYGB regained all lost weight during a two-week brain infusion of the MC4R-antagonist SHU9119, and then fell back to the lower body weight level after termination of the infusion [261]. As the lateral ventricle infusions most likely acted on forebrain sites, it is plausible that they affected primarily MC4R-signaling of basomedial hypothalamic POMC and AGRP neurons with their widespread forebrain projections. It is interesting to speculate that SHU9119 inhibited MC4R-signaling augmented by endogenously elevated levels of GLP-1,

as GLP1R-bearing POMC neurons respond to both locally administered GLP-1 and systemically administered semaglutide, which in turn activate LPBN neurons directly or via inhibition of inhibitory AGRP neurons [128]. This scenario is also supported by the observation in mice that the weight loss-induced up-regulation of AGRP neurons seen with dietary restriction is not seen with RYGB-induced weight loss [121].

Melanocortin-signaling at the level of autonomic neural outflow may also be involved as shown by rescuing MC4R expression selectively in autonomic neurons in mice with whole body knockouts [260]. Most of the RYGB effects on weight loss and glycemic control were abrogated in whole body MC4R knockout mice. However, MC4R-expression restricted to cholinergic preganglionic autonomic neurons (both vagal and sympathetic) largely rescued these effects [260]. Because the RYGB model used by these investigators was characterized by major changes in energy expenditure (although not corrected for body weight) rather than energy intake, the findings point to MC4Rs on preganglionic sympathetic neurons innervating adipose tissue [262].

4.1.4.3. Insulin-like growth factor binding protein-2 (IGFBP2). Deletion of insulin-like growth factor binding protein-2 (IGFBP2), which is significantly increased after RYGB in humans, rats and mice, led to approximately 30% less RYGB-induced weight loss compared to wild type mice [194]. This suggests that IGFBP2-signaling is required for the full beneficial effects of RYGB in mice. Interestingly, insulin-like growth factor-1 (IGF-1) is also significantly increased in all limbs of the GI-tract 2 weeks after RYGB in rats [40], and IGF-1-induced intestinal proliferation is inhibited by insulin-like growth factor binding protein-4 (IGFBP4) [263]. Whether IGFBP2 has similar inhibitory effects on IGF-1 induced intestinal proliferation remains to be determined, but the fact that IGFBP2-deficiency did not prevent the RYGB-induced increase in total intestinal wet weight 20 weeks after surgery [194] argues against it.

4.2. Mechanisms affecting primarily energy expenditure and feed efficiency

Some hypothesized mechanisms are restricted to the gut itself, but most of them embrace changes in gut-brain communication and resulting changes in eating behavior and autonomic control of critical organs and tissues.

The major non-neural mechanism purported is the re-programming of gut metabolism towards energetically demanding processes, thereby drastically reducing feed efficiency and body weight [39,112,113]. In addition, changes in peripheral glucose, lipid, and amino acid metabolism could have beneficial effects on plasma glucose and triglyceride levels independent of weight loss [14,39,61]. However, because of the descriptive and associative character of all these studies, direct evidence for the requirement of such mechanisms in the beneficial effects of bariatric surgery is missing. Not knowing the exact nature/molecular identity of the critical steps within these pathways, it has been difficult to bring them to the test. It needs to be demonstrated that interfering with or preventing the hypothesized re-programming abrogates the RYGB or VSG-induced beneficial effects.

Another hypothesized mechanism thought to primarily improve glycemic control through peripheral mechanisms is the bariatric (metabolic) surgery induced suppression of an unknown anti-incretin hormone or factor secreted from the proximal intestine that normally is responsible for the obesity-associated diabetic state [264–266]. However, without knowing the identity of such a hormone or factor, it will be difficult to prove this hypothesis.

5. WEIGHT LOSS-DEPENDENT VS. WEIGHT LOSS-INDEPENDENT EFFECTS

Weight loss through dieting and other behavioral modifications is extremely effective in improving metabolic and general health, including diabetes, hepatic steatosis, cardiovascular parameters, cancer susceptibility, sleep, sexual drive, and quality of life. It is now almost 20 years since a randomized controlled trial in subjects with obesity demonstrated that losing just 5–10% of body weight through dieting and lifestyle changes significantly reduces diabetes susceptibility by over 50% [267], and more recent studies have fully confirmed these findings [268]. However, while the highly beneficial effects of dieting in subjects with obesity are uncontested, the problem is sustaining these benefits with continued behavioral changes over the rest of a 20 or 30 year-old's life expectancy of 50–70 more years in an obesogenic environment. It has been estimated that falling into recidivism amounts to 80% or more of subjects dieting. This is where the true value of bariatric surgery is evident, as surgery makes it easier to adhere to behavioral and lifestyle changes over much longer periods of time. Surgery prevents this recidivism by largely preventing the adaptive counter-regulatory responses to weight loss, namely increased hunger and hypometabolism, and current evidence points to key mechanisms acting on food intake and re-setting energy balance in the brain.

When compared head-to-head, it also became clear that using caloric restriction to match the weight loss of bariatric surgery resulted in the same metabolic benefits, specifically improvements in fasting glucose and insulin, glucose tolerance, and insulin sensitivity/resistance. This was demonstrated in several clinical studies varying in length between 10 days and 23 weeks [82,269–273], and in several rodent studies [112,189,194,223,260]. It is important to note that these metabolic benefits are also induced by a hypocaloric state, as extended fasting can rapidly and significantly improve metabolic function (for a recent review and meta-analysis see [274]). In the most comprehensive and technically sophisticated study in patients with obesity randomized for BMI as well as severity and duration of diabetes, the authors concluded that "the metabolic benefits of gastric bypass surgery and diet were similar and were apparently related to weight loss itself, with no evident clinically important effects independent of weight loss" [82]. Clearly, weight loss-independent effects, such as a greater decrease in branched-chain amino acids, an increase in plasma bile acids, and greater changes in the gut microbiome after gastric bypass were confirmed, but these changes were not associated with greater improvements in metabolic function [82].

Nevertheless, some clinical studies provide evidence for weight loss-independent effects of bariatric surgery on glycemic control [see [275] for recent review) and major adverse cardiovascular events based on post-hoc statistical adjustments for weight loss [276]. Some pre-clinical studies also provide evidence for weight loss-independent effects on glycemic control [14,277,278] and hepatic steatosis [242], based on pair-feeding or weight-matching that resulted in similar weight loss. However, the "additional" weight loss-independent effects were generally small compared to the weight loss-dependent effects. Thus, the term "metabolic surgery" seems premature at this time for several reasons. The major reason is the lack of strong evidence for major weight loss- and hypo-alimentation-independent effects, which is often the result of studies without proper controls. Claims of weight loss-independent beneficial effects are difficult to make when there is no control group in which dietary intake and weight loss are matched to be the same as in surgery patients. This is not to say that weight loss-independent effects do not exist, it merely suggests that they are

less powerful and potentially less important than the major effects driven by weight loss overall. Thus, well-spent research funds should have the goal to focus on a better mechanistic insight how bariatric surgery leads to weight loss and to a suppression of counter-regulatory responses that lead to weight regain with dieting or behavioral treatments for obesity. Regardless, it is very likely that bariatric surgery induces novel signaling mechanisms that may be truly independent of weight loss and hypo-alimentation that will be identified in the future.

6. CONCLUSIONS

Bariatric surgery is currently the most effective treatment for severe obesity, and has tremendously increased the quality of life for thousands of patients. In contrast to pharmacological treatments the intervention is restricted in time but typically lasts for decades. For logistical reasons, however, it will not be possible to deliver bariatric surgery to the larger population. Therefore, learning from mechanisms that make these operations so effective is a major goal in obesity research. The relatively young science of bariatric surgery has tremendously stimulated metabolic research and generated several lead hypotheses as to their mechanism of action. A healthy level of skepticism by many basic scientists together with the can-do attitude of many surgeons has created a competitive atmosphere and fertile ground for out-of-the-box thinking.

Although no clear and unique mechanism has yet emerged, there is moderately convincing evidence that increased GLP-1 signaling plays a significant role in orchestrating reduced food intake and loss of body weight after RYGB in humans, and in improving glucose homeostasis after RYGB and VSG in rodents and humans. There is also some evidence from transgenic mouse models for the partial involvement of other signaling pathways, including bile acids, gut microbes, leptin, melanocortin, and IGFBP2. However, besides perhaps melanocortin signaling, none of these signaling pathways seems to account for the bulk of the beneficial effects of bariatric surgery. We speculate that, similar to the genetics of obesity, dozens of signaling pathways contribute to these beneficial effects, each with a small size effect and making their experimental demonstration difficult. This was quite unexpected because the initial intervention in bariatric surgery is limited to the gut. If correct, the scenario reveals a much richer cross-communication between the gut and the rest of the body, at least as far as body weight regulation is concerned. As with the genetics of obesity, it is still possible that we are currently missing a signaling pathway(s) with a larger size effect, as methodological advances in clinical and preclinical research become available.

6.1. Lessons learned

1. The complexity and redundancy of gut-brain communication and brain control of food intake and energy balance are more appreciated. It seems unlikely that the elusive mechanism mediating the effects of bariatric surgery involves a single pathway, but instead likely consists of multiple signaling pathways (cascades). This view is supported by the recent push towards multi-pharmacy specifically capitalizing on gut hormones.
2. Gut-brain circuits can be exploited to change brain function and are potential therapeutic targets and gateways into the brain. Administering drugs and manipulating the periphery is far easier than trying to directly target the brain.
3. We should be aware that significant differences may exist between clinical and pre-clinic bariatric surgery models, and that animal models need to be standardized and well-validated.
4. Ask the right question. Not every change observed after a particular surgery leads to a valid hypothesis. Carry out appropriate controls such as pair-feeding and/or weight-matching before formulating a hypothesis.
5. Choose the best animal models for specific operations and hypotheses. Reversal of obesity vs. prevention of obesity. Obese diabetic vs. non-obese-diabetic.

6.2. Future directions

The most promising hypotheses (e.g. the involvement of microbiome, hormone, and bile acid signaling) should be tested with advanced techniques, including inducible, tissue-specific knockout models, both rat and mouse, and with some humanized physiological traits (e.g. bile acid or lipid profile etc.) if possible. Applied to neural gut-brain communication pathways, state-of-the-art neural manipulation techniques should be used. Among these are manipulations (stimulation, inhibition, or silencing) of function-specific vagal or dorsal root afferents and neuron populations in the brain in verified genetic mouse lines. Mouse RYGB surgery should be further developed and practiced in dedicated surgery cores to reduce mortality and replicability.

However, investing in the prevention of obesity and metabolic disease seems unavoidable if we are to stem the tide. Globally, an estimated 39 million children under the age of 5 were overweight or obese in 2020 and knowing the high fidelity progression from childhood overweight to adult obesity is particularly alarming and suggests that prevention should be the first choice in stemming this global crisis. The fact that this insight and recommendation was already available 50 years ago [22] seriously questions the ability of our scientific and political institutions to act (David L. Katz, Time Magazine, May 30, 2017). We need to collectively find the political will to make fundamental changes to the environment, education, food industry, and agricultural policies.

AUTHOR CONTRIBUTIONS

Vance Albaugh: Conceptualization, Data Curation, Validation, Writing — original draft, Writing — review and editing. **Yanlin He:** Writing — review and editing. **Sangho Yu:** Writing — review and editing. **Heike Munzberg**: Writing — review and editing. **Christopher Morrison:** Writing — review and editing. **Hans-Rudolf Berthoud:** Conceptualization, Writing — original draft, Writing — review and editing, Visualization.

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CONFLICT OF INTEREST

None of the other co-authors declare any conflict of interest.

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