DR DARLEEN SANDOVAL (Orcid ID : 0000-0003-3669-3278)

Article type : Review Article

Corresponding author mail id:- darleens@umich.edu

Mechanisms for the metabolic success of bariatric surgery

Darleen A. Sandoval, PhD

University of Michigan, Ann Arbor, MI USA

Address for Correspondence:
Darleen Sandoval, Ph.D.
University of Michigan
Department of Surgery
2800 Plymouth Rd
Ann Arbor, MI, 48109

Abstract

Bariatric surgery is our most effective strategy, to date, for the treatment of obesity and its comorbidities. However, given the enormity of the obesity epidemic, and sometimes

variable results, it is not a feasible strategy for treatment for all obese patients. A simple Pubmed search for “bariatric surgery” reveals over 28,000 papers that have been published since the 1940’s when the first bariatric surgeries were performed. However, there is still an incomplete understanding of the mechanisms for the weight loss and metabolic success of surgery. Understanding the mechanisms is important as it may lead to greater understanding of the pathophysiology of obesity and could lead to surgery-alternative strategies for treatment of all obese patients. In this review, the potential mechanisms that underlie the success of surgery with a focus on potential endocrine, neural, and other circulatory factors (eg. bile acids) that have been proposed to play a role are discussed.

Introduction

Bariatric surgery is currently our most effective strategy for sustained weight loss and improvements in the metabolic co-morbidities of obesity. Weight loss averages ≥30% over 10 years and leads to a 40% remission of type 2 diabetes mellitus (T2DM)[1,2], often allowing complete discontinuation of T2DM-directed medications. No other treatment can claim this kind of remission of T2DM. The most popular bariatric surgeries worldwide are vertical sleeve gastrectomy (VSG) and roux-en-Y gastric bypass (RYGB)[3]. After RYGB, ingested food bypasses ~95% of the stomach, the entire duodenum, and a short portion of the jejunum. VSG, a distinct surgery in which 80% of the stomach along the greater curvature is removed with no intestinal rearrangement, is the most common bariatric procedure performed in the United States (58 vs. 19% of total surgeries for VSG vs. RYGB, respectively[4]; see Figure 1 for schematic of each surgery). Regardless of the success of bariatric surgery, the invasiveness and the infrastructure required to perform surgery continues to drive the need to find alternative strategies to treat obesity and T2DM.

The most simplistic hypothesis for the benefits of VSG is that a smaller stomach physically restricts meal size leading to weight loss and improved metabolic endpoints secondary to weight loss. However, data in humans and rodents both demonstrate changes in feeding behavior that go beyond mechanical restriction of meal size. Indeed, we have generated considerable data in our rodent model of VSG that challenge this hypothesis. We find sustained weight loss and decreased body fat but preserved lean

mass with VSG alongside an early post-operative reduction in food intake[6]. While the reduction in food intake might suggest a restrictive mechanism, food intake returns to the level of sham animals ~2-weeks postoperatively. Further, if exposed to a period of food-restricted weight loss, VSG animals become as hyperphagic as sham animals when returned to ad lib access to food[6]. In another physiological model of hyperphagia, lactating female rodents who have had VSG increase feeding to the same extent as sham surgery females[7]. These latter two studies demonstrate that any hypothesized physical restriction does not prevent hyperphagia when the physiology demands it. Lastly, VSG animals consistently avoid calorically-dense high-fat foods indicating that they are not attempting to overcome physical restriction by choosing more calorically-dense foods[8,9]. In humans[10,11] and rodents[12], nutrients rapidly empty from the pouch or sleeve from RYGB and VSG surgeries, respectively, further supporting that mechanical restriction does not play a role in surgery-induced reductions in feeding. Thus, the data suggest that the mechanisms that drive the success of bariatric surgery are physiological in nature. This review will discuss the potential mechanisms that underlie the success of surgery with a focus on what has been learned from rodent models.

Comparisons of clinical and pre-clinical outcomes

Preclinical work offers the ability to study cellular and molecular mechanisms that drive the success of surgery. However, there are always important issues to consider when comparing rodent to clinical data. Despite this, the outcomes of surgery are qualitatively very similar between rodents and humans.

Physiologically, both humans and rodents have sustained reductions in body mass, changes in feeding behavior including meal patterning, food reward, and macronutrient preference, rapid nutrient entry into the intestine, large postprandial increases in gut peptides including GLP-1, increases in circulating bile acids, and changes in the microbiome (see below for details). That being said, there are potential critical differences. Most simplistically and not suprisingly, the timing of changes in body weight and food intake differ. The body mass and food intake nadir is typically 2-3 weeks in rodents and 6-12 months in humans. The majority of this weight loss in rodents is fat, rather than lean mass[13]; whereas humans lose both lean and fat mass[14]. In regards to food intake, humans seem to have sustained reductions in food intake that

are reported up to 10y post-operatively[15], whereas rodents return to ingesting similar caloric loads as sham surgery animals 2-3 weeks after surgery[6]. However, the persistently lower food intake in humans may actually reflect the intake that is appropriate to maintain energy balance for the new lower body mass. It is also worth mentioning that assessment of food intake in humans is confounded by experimental error given that dietary recall consistently results in under-reporting but also by the fact that patients undergo pre- and post-surgical feeding behavior counseling. Thus, in humans, the ability to understand the biological impact of surgery on food intake is limited.

Regardless, if we assume that food intake is persistently reduced in humans, then another species difference is highlighted by the fact that recent work in mice suggests that the maintenance of weight loss in mice after RYGB may be largely due to increased energy expenditure rather than reduced food intake[16]. In contrast, changes (either increases or decreases) in energy expenditure are not consistently reported after VSG in rodents [6,17]. This, again, is in contrast to humans who have reported reductions in energy expenditure after both RYGB[18] and VSG[19]. However, this reduction in energy expenditure could be in response to the reduced caloric intake or it may reflect surgery-induced changes in body composition rather than a direct effect of surgery on energy expenditure[19–21]. That being said, assessment and interpretation of changes in energy expenditure are constantly being debated in both humans and rodents. Regardless of the challenges, there is value in using animal models to understand the biological impact of surgery on these endpoints and in generating targets for the mechanisms underlying the success of surgery.

Mechanisms for metabolic success

The role of gut-secreted peptides

That a change in GI anatomy could cause such a rapid and sustained weight loss with the associated improvements in co-morbidities underscores the tremendous impact of the GI system in regulating homeostasis. However, the exact mechanism(s) driving the weight loss and metabolic improvements still remain elusive. One hypothesis that persists is that bariatric surgery increases nutrient-induced secretions of GI-tract

peptides that have been shown to play a role in regulating appetite, energy expenditure, and blood glucose homeostasis.

Satiety-regulating peptides

Specialized enteroendocrine cells secrete peptides in response to changes in nutrient status. Glucose-dependent insulinotropic peptide (GIP) and glucagon like peptide-1 (GLP-1) secreted from predominantly the upper and lower small intestine, respectively, are thought to be important for regulation of glucose homeostasis while cholecystokinin (CCK), GLP-1, glucagon like peptide-2 (GLP-2), oxyntomodulin, and peptide YY (PYY) also function as satiety signals[22]. GIP is secreted from enteroendocrine K-cells located within the proximal gut and is critical for regulation of insulin and gastric secretion and motility. Although traditionally these enteroendocrine cells were thought to be differentiated by the peptides they secrete, it is most likely that the differentiation is regional[23–25]. An example of regional distinction is that GLP-1-secreting cells in the distal jejunum and ileum co-express PYY[26], while proximal GLP-1-secreting cells co-express CCK, GIP, neurotensin, or secretin[27]. Although traditionally these enteroendocrine cells were differentiated by the peptides they secrete, recent research suggests that there is heterogenous co-expression of different peptides in these cells, and that these patterns of co-expression differ between regions of the gastrointestinal tract[28]. This process mayenable enteroendocrine cells to respond to specific local nutritional stimuli[29]. Bariatric surgeries change both the GI anatomy but also the rate at which nutrients enter the intestine. Thus, it is not surprising that many of these gut peptides are also altered by bariatric surgery.

Ghrelin is secreted from gastric and duodenal enteroendocrine cells; it is one of the few GI tract-secreted peptides for which circulating levels decrease postprandially. Increased circulating ghrelin levels are associated with increased, rather then reduced, drive to eat[30]. With RYGB, ghrelin levels are maintained in many studies while with VSG they are consistently decreased[31,32] suggesting that although the stomach and duodenum are no longer receiving luminal nutrient stimuli with RYGB, the blood flow to the tissue is enough to stimulate the release and maintain plasma ghrelin levels. To determine whether the decrease in ghrelin with VSG is necessary for the success of surgery, VSG was performed in mice genetically devoid of ghrelin[33]. However, these

mice lost body weight and improved their glucose tolerance as much as sham surgery controls. Together with the slightly superior improvements in body weight and glucose homeostasis with RYGB vs. VSG, these data suggest that a reduction of ghrelin, in and of itself, is not necessary for metabolic improvements after bariatric surgery.

Whether cholecystokinin (CCK), an anorectic peptide secreted from the upper GI tract, increases after bariatric surgery is not clear. Although CCK has been found to be increased in RYGB, this increase seems to be greater after VSG in humans[34,35]. However, Otsuka Long-Evans Tokushima Fatty (OLETF) rats lacking CCK-1 receptors, are able to lose weight and improve glucose homeostasis in response to RYGB[36] suggesting that CCK signaling is also not necessary for the metabolic success of bariatric surgery, or at least in response to RYGB.

Peptide YY (PYY) and GLP-1 are secreted from distal L-cells and both peptides increase postprandially after VSG and RYGB in humans and rodents[10,37–41]. While consistent increases in PYY are seen after surgery, its mechanistic role in the weight loss associated with bariatric surgery has not been studied as extensively as GLP-1. One study has shown that PYY KO mice lost less weight acutely after RYGB (assessment at 10d postoperatively)[42]. Unfortunately, these mice were not assessed further for changes in feeding behavior.

Both total and active levels of GLP-1 are increased after surgery. Postprandial GLP-1 levels are strikingly (~10-fold) increased after both RYGB and VSG and this increase is seen within 2 d, and is maintained for at least 2 y after surgery[10,35,43–45]. Importantly, weight loss through caloric restriction does not lead to an increase in postprandial GLP-1 levels like VSG and RYGB[45] highlighting the physiological effect of these surgeries. Preproglucagon is the gene that produces GLP-1 but it also produces other peptides and based on post-translational processing this occurs in a tissue-specific fashion. In the intestine and CNS, expression of prohormone convertase 1/3 processes preproglucagon peptides to produce GLP-1 and oxyntomodulin which are both thought to regulate satiety and glucose homeostasis, and GLP-2 which regulates intestinal growth and morphology. Circulating levels of all of these peptides are increased by bariatric surgery[38,46,47]. Preclinical studies in rats demonstrate that the increase in GLP-2 occurs in parallel with intestinal hypertrophy after RYGB[48]. However,

mice null for the GLP-2 receptor lose weight and improve glucose tolerance similar to WT animals in response to VSG[49]. Given its link to glucose sensing and absorption in the gut[50], the increase in GLP-2 with RYGB could also blunt some of the macronutrient malabsorption that would be expected to increase with intestinal rearrangement, an effect minimized with VSG. Thus, these apparent differences could reflect the varied impact of the specific surgeries or it could simply be that the increase in GLP-2 and consequent increase in hypertrophy that occurs with RYGB is a marker, but not a mechanism of the success of surgery.

PYY is activated by a cleavage enzyme, dipeptidyl peptidase-4 (DPP4). This same peptide degrades and inactivates GLP-1. To determine the role of these two anorectic peptides in regulating feeding after RYGB, one study administered, saline, a DPP4 inhibitor, a GLP-1 receptor antagonist, or a combination of the DPP4 inhibitor plus the GLP-1 receptor antagonist to patients 3 months after RYGB[51]. Only the combined drugs significantly increased the amount of food ingested during the standardized meal, suggesting that both PYY and GLP-1 receptor signaling are necessary to regulate acute meal ingestion after surgery. Altogether, these data suggest that the combined impact of these anorectic peptides is more important than the impact of any one peptide alone.

In the pancreas, predominant expression of proconvertase 2 leads to preproglucagon processing to produce glucagon. While some studies have reported an increase in postprandial glucagon after RYGB[52–55], a later study suggested that this work was confounded by the fact that RYGB causes large increases glicentin, another preproglucagon peptide that has increasing cross-reactivity with standard glucagon ELISAs with increasing plasma concentrations[56]. Thus, more research is needed from independent groups utilizing sensitive and specific assays to determine whether glucagon is increased with surgery or not. Regardless, if glucagon does go up, it may not be critical in the success of surgery as genetic deficiency of both the glucagon receptor and the GLP-2 receptor does not blunt the metabolic benefits of VSG[49].

Oral glucose drives a much greater insulin response compared to when the same glucose load is administered intravenously[57]. This incretin effect is attributed to GLP-1 and glucose-dependent insulinotropic peptide (GIP)[58,59]. In healthy and T2DM subjects,

GLP-1 and GIP contribute nearly equally to the incretin effect stimulating the majority of postprandial insulin release[58]. Instead, the defect with obesity and T2DM seems to be in an overall reduction in the incretin effect[60]. Both RYGB and VSG correct and even enhance the incretin effect. Both GLP-1 and GIP are also rapidly degraded by DPP4, the same cleavage peptide that activates PYY. DPP4 inhibitors increase GIP and GLP-1 two-fold. When administered with or without exendin 9-39, DPP4 inhibitors improve glucose tolerance and insulin secretion in non-surgical T2DM patients[61]. In mice, DPP4 inhibitors retain their glucose improvement efficacy when either GLP-1R or GIPR are genetically deficient but not in double GLP-1R/GIPR KO mice[62]. Together these data suggest that either GLP-1 or GIP receptor signaling is sufficient for the ability of DPP4 inhibitors to improve glucose tolerance. However, in T2DM patients that have had RYGB a DPP4 inhibitor failed to improve glucose tolerance or β-cell function while GLP-1 receptor signaling was blocked[63] suggesting that RYGB shifts the balance of the incretin effect toward GLP-1 and away from GIP. Interestingly, GIP does not show consistent increases after RYGB[45,64] and even has demonstrated decreases 1 year after both RYGB[65] and VSG[32]. Together these data suggest that postprandial increases in GLP-1 are more important than GIP in regulating the changes in postprandial insulin and consequently glucose after bariatric surgery.

Despite the indication that GLP-1 is important for postprandial changes in glucose homeostasis, whether the increase in GLP-1 is necessary for weight loss or T2DM resolution remains to be seen. One of the complications of determining the mechanistic role of GLP-1 in mediating T2DM resolution is that the duration of disease and consequently the degree of impairment of β-cell function prior to surgery, may be more critical in determining whether those β-cells can recover sufficiently to resolve T2DM[66]. While one study found a predictive role of the degree of increase in GLP-1 and in the remission of T2DM after RYGB[41], another study found no such relationship after VSG[67]. Still, administration of the GLP-1 receptor antagonist, exendin 9-39, impaired the insulin response to an oral glucose load in both humans and rodents after bariatric surgery[43,68–70] suggesting a role for GLP-1 in postprandial insulin secretion. However, in dietary-induced obese mouse models genetically deficient in GLP-1 receptors, both VSG and RYGB retain their ability to induce weight loss and improve

glucose[71–73]. Lastly, inducible knockdown of the β-cell GLP-1 receptor in adult mice using the Cre-loxP system prevented improvements in glucose tolerance and glucose-stimulated insulin secretion, but not weight loss[74] in one study, but there was no impact of a similar genetic disruption on VSG results in another[75]. A recent study with data from lean post-gastrectomy patients with postprandial hypoglycemia and a lean VSG mouse model confirms previous studies that pharmacological blockade of GLP-1 receptor signaling increases glucose and reduces postprandial insulin responses[76]. While it is true that impaired insulin resistance could confound the ability to detect a role of GLP-1 in surgical success in mice, there are several problems with extrapolating these recent data to suggest that GLP-1 is critical for T2DM resolution. First, the extent to which the altered glucose responses to a meal after surgery are responsible for T2DM is not clear. In fact, some argue that an increase in glucose variability as is seen with bariatric surgery has detrimental effects including increased cardiovascular risk[77]. The other issue is the interpretation of pharmacological data. Blockade of GLP-1 receptor signaling increases the glucose curve in both sham and surgery animals or control vs. RYGB patients. In one clinical study where RYGB patients were treated with Ex9 during a meal, the glucose area under the curve values of the Ex9-treated patients were expressed relative to vehicle and the impairment was not statistically different between control and RYGB patients[78]. Thus, the interpretation of these pharmacological studies are complicated and leave an open question as to whether GLP-1R signaling matters specifically for T2DM resolution after surgery, or whether it just generally matters for insulin regulation whether the patients have had surgery or not.

Although surprising that the 10-fold increase in plasma GLP-1 with surgery might not play a critical mechanistic role in the success of surgery, it is possible that this increase reflects a defensive response of the intestine to the rapid nutrient entry induced by both surgeries. Clearly, the changes in GI anatomy with surgery greatly alter the cocktail of postprandial gut peptides. Although these changes, in particular with GLP-1, have been found to be associated with greater weight loss, association does not mean causation. Alternatively, it may be that changes in the whole cocktail of gut peptides is necessary for the response to bariatric surgery explaining why genetic

removal of signaling for one gut peptide at a time has minimal effect. More work will be needed to understand whether the changes in these gut peptides are a marker or a mechanism for the success of surgery.

The role of the nervous system:

Feeding behavior is carefully regulated by the CNS and given the clear changes in feeding behavior with surgery, it would follow that the CNS is mediating these changes. Feeding patterns are clearly and persistently altered by bariatric surgery with both humans and rodents ingesting smaller more frequent meals post-operatively[79–85]. In addition, bariatric surgery alters taste sensitivity, food reward and macronutrient preference in rodents[8,9,86,87]. In regards to the latter, lean and obese rats and mice will overwhelmingly ingest fat when given a choice between fat, carbohydrate, and protein macronutrients[6,9]. However, bariatric surgery shifts this preference towards carbohydrate and away from fat[6,9,87,88]. In humans similar shifts in food preference are observed[89]. An interesting possibility is that the reduced appetite or shift in macronutrient preference seen with bariatric surgery is not because some foods are found to be more favorable than others but because ingestion of certain foods leads to aversive side-effects. Many patients report feelings of food-induced sickness after either RYGB or VSG[90,91]. In fact, greater weight loss is correlated with reports of greater food-induced aversion[91]. Similarly, rats have a particular aversion to oil after both RYGB[92] and VSG[9].

In addition to changes in feeding behavior, there are multiple points of data that indicate that the brain is more highly activated after a meal following bariatric surgery. For example, we have found that FOS-like immunoreactivity, a marker for neuronal activation, within a specific area of the hindbrain, the nucleus of the solitary tract (NTS) and the area postrema (AP), increases after a sucrose or an equi-caloric lipid gavage to a greater extent in male rats that have had VSG vs. rats that had sham surgery and were either ad lib or pair-fed (PF) to the VSG animals[8]. The NTS and AP, are critical junctures between the vagus and blood stream, respectively. In fact, data suggest that it is not just the signaling to this region that is altered but that the electrical properties of neurons within the NTS that are altered by high fat diet and this effect is reversed by RYGB[93]. In patients that have received RYGB, the hypothalamus, pituitary, and medial

orbital cortex were all more highly activated and the right dorsolateral frontal cortex were more deactivated after a meal[94].

A critical question is what are the key signals that drive this increase in CNS activation with surgery? The increase in circulating hormones/gut peptides (many of which have receptors throughout the CNS) and/or nutrients could be acting directly within the CNS to initiate these responses. However, at this time there is limited data to support that direct hormone and/or nutrient action drives greater CNS activation. While GLP-1 receptor expression within the CNS has been shown to be important for regulation of body mass, central nervous system administration of exendin 9-39, a potent GLP-1 receptor antagonist, in rats does not block the impact of RYGB on weight loss[73] suggesting that CNS GLP-1 receptor signaling is not critical for surgery-induced weight loss. However, it is possible that peripheral nerve GLP-1 receptor signaling overrides the CNS antagonism and/or that GLP-1 receptor signaling works in concert with other gut peptides (e.g. PYY) in order to regulate feeding. In addition, due to increased “gastric” or sleeve emptying rate, nutrients enter the intestine much more rapidly. This clearly changes the pattern of nutrient responses to a meal. For example, continuous glucose monitoring in patients after RYGB shows a greater dynamic range in glucose levels with larger peaks but rapid returns to baseline after a carbohydrate-rich meal[95]. Whether these greater peaks could contribute to greater postprandial CNS activation remains to be determined.

Another possibility is that the nutrient levels themselves or the concomitant rise in gut peptides increase vagal afferent firing which then feeds back to higher brain centers. Additionally, the increased gastric pressure, that drives the increase in emptying rate with VSG[12] could provide greater mechanical feedback via the vagus to the CNS. A standard approach to examining the neuronal component of the gut-brain axis is to surgically ablate the vagus. Neither hepatic branch[96] or subdiaphragmatic[97] vagotomy impact surgical weight loss. However, subdiaphragmatic vagotomy did blunt surgery-induced shifts in taste preference, and the mechanism is thought to be due to alterations of dopamine signaling within the CNS[97]. In addition, when the vagus is ligated at the stomach, RYGB is less effective than when the nerve is left intact[98]. Lastly, ablation of the vagal branch that innervates the intestine (celiac branch

vagotomy) also blunts surgery-induced weight loss and suppression of feeding in response to RYGB[99]. Altogether, these data support a specific role for intestinal rather than hepatic vagal innervation in the success of surgery. Like distinct nuclei within the CNS, the vagus is a heterogenous population of neurons[100–102] allowing individual neurons to respond to distinct stimuli. Indeed, activation of specific neurons within the nodose ganglia, the cell body of the vagus, have been found to differentially regulate GI functions. For example, optogenetic activation of vagal neurons that express GLP-1 receptors regulate gastric stretch, while activation of neurons expressing a specific nutrient sensing G-coupled protein receptor, GPR65, regulate intestinal nutrient sensing[102]. The application of this technology to surgery will be an important to move towards a better understanding of the role of the vagus in mediating the various physiological responses to bariatric surgery.

The role of Intestinal morphology

The intestine forms a critical barrier from the external to internal environment. Perhaps because of this critical function, there is a very high turnover (every 4th day) of the epithelial cells that make up this barrier. These cells line the villi (absorptive region) and crypts (the region where the stem cells, the precursors for intestinal epithelial cells, are located). Nutritional state and intestinal diseases both impact intestinal morphology (villi length and/or crypt depth); for example, obesity has been found to increase both of these variables[103]. However, RYGB has also been found to increase overall intestinal thickness, both villi length and width, crypt depth, and mucosa volume within the roux and common but not in the bilipancreatic limb[48,104–106]. The lack of proliferation in the biliopancreatic limb suggests a role of nutrient exposure (or lack thereof) in directing these regional differences. Interestingly, data suggest that after RYGB, the intestine directs glucose towards the hexosamine biosynthesis pathway, a metabolic pathway critical in tissue growth[107].

The impact of VSG on intestinal morphology is less clear. One paper reported no impact of VSG on intestinal morphology[104] and others demonstrate an increase in villus length but not crypt depth[108–110]. Also unlike RYGB, VSG increases the number of GLP-1 positive cells within the jejunum and ileum[108,110]. This would suggest that VSG drives an increase in production of GLP-1 positive cells. Given that the plasma levels of other

gut peptides (CCK, GIP) are also increased by VSG, these data suggest that there is an overall increase in enteroendocrine cell production. However, more work is needed to differentiate the impact of changes in the response of these enteroendocrine cells to nutrients vs. the increase in cell number and their respective contribution to the overall increase in gut peptide levels and of course whether these differences matter to the overall success of surgery.

The role of changes in bile acids

Bile acids (BA) are synthesized by the liver and travel from the liver to the gall bladder, bile duct, intestine, blood, and finally are transported back into the liver. Primary BA produced by the liver can be conjugated with either glycine or taurine. Once in the lumen of the intestine, the intestinal flora modifies primary BA to form secondary BA. Changes in BA have been linked to changes in glucose homeostasis. For example, fasting plasma levels and specifically increased levels of cholic acid, deoxycholic acid, and their conjugated forms are found in insulin resistant patients[111] and elevated fasting levels of total BA with preferential increases in more hydrophobic and conjugated BA are found in T2DM patients[111–113]. Interestingly, RYGB patients who have profound improvements in glucose homeostasis also have been found to have a >3-fold increase in plasma BA as compared with weight-matched nonsurgical controls[114]. Specifically, RYGB in humans increases cholic acid (CA), chenodeoxycholic acid (CDCA) (primary BA), and deoxycholic acid (DCA; a secondary BA)[115–119]. The difference in BA between bariatric surgery and impaired glucose metabolism may reside in differences in the ratio of the various BA species. For example, one study demonstrated that a higher proportion of CDCA relative to total bile acids (CDCA%) and a shorter duration of diabetes was predictive of surgery-induced remission of T2DM in Chinese patients[120]. Similar effects on BA increases are observed after bariatric surgery in animal models[109,121,122]. In mice, VSG also results in a change in the composition of BA also towards CA, but there is also an increase in tauroursodeoxycholic acid (TUDCA)[95], a particular BA that has been found to have potent metabolic effects in a diabetic mouse model[123]. Interestingly, ursodeoxycholic acid, a hydrophilic secondary BA utilized pharmacologically to treat cholestasis, has no additional impact on gut peptide or glucose levels when administered to RYGB patients[124]. Thus, the differences in the

impact of obesity and bariatric surgery are important as different types of BA have differing metabolic properties and differing affinities (including antagonistic properties) for the two receptors thought to be critical for BA signaling.

In addition to their emulsifying properties, BA also act as hormones with two different identified receptors; a cell surface membrane-bound G protein-coupled receptor (TGR5)[125], and a nuclear transcription factor, farnesoid X receptor (FXR)[126,127]. TGR5 activation within the intestine increases secretion of GLP-1 from intestinal L-cells[128], and within the muscle and brown adipose tissue it increases energy expenditure[129]. FXR, which is highly expressed in the liver, intestine, kidney, and adrenal glands, has been found to be a crucial upstream regulator of lipid and glucose metabolism, and of BA synthesis[130–132].

Intestinal activation of FXR results in the upregulation of fibroblast growth factor 19 (FGF19; FGF15 is the mouse ortholog) synthesis and secretion. In turn, circulating FGF19/15 regulates hepatic BA synthesis and stimulates gall bladder filling. FGF19/15 improves glucose homeostasis specifically by inhibiting hepatic gluconeogenesis[133], enhancing hepatic mitochondrial activity and glycogenolysis[134,135], and increasing insulin-independent glucose uptake[133] and does so by activating multiple fibroblast growth factor receptors in multiple target organs including the liver, pancreas, adipose, and brain[136]. Demonstrating translational relevance of these findings, patients with T2DM have reduced FGF19 levels[113] and RYGB increases FGF19, an effect that has been linked to the surgery-induced T2DM remission[118,137,138].

Of course association does not mean causation so preclinical studies have been carried out to determine whether BA signaling is necessary for the success of surgery. With TGR5, the data are conflicting. One study found that TGR5-KO mice demonstrated similar weight loss compared to sham surgery animals but the degree of surgery-induced improvements in both glucose tolerance and hepatic triglycerides was blunted[139]. These mice also retained the postprandial increase in GLP-1. While another paper also found that TGR5-KO mice had blunted improvements in glucose tolerance and hepatic triglycerides, they also found that these mice did not lose weight, had blunted energy expenditure and postprandial increases in GLP-1[140]. It is unknown what factors contribute to these differences. Both papers used mice that were generated by

Merck[141] although mice were purchased from Taconic for one paper[139] and were received directly from Merck[140] in the other. There are methodological considerations as well. The age of the animals when placed on the high fat diet (HFD), the type and amount of time the animals were on HFD, and the amount of time the animals were studied after surgery differed between the studies. This latter point might be important as both studies report early weight loss after VSG regardless of genotype but the TGR5KO animals that had VSG regained body weight in the paper by Ding et al.[140] at a time point that was later than the time point for which the animals were sacrificed in the paper by McGavigan et al.[139]. Lastly, although it is difficult to tell based on the reported methodology, differences in surgical technique could also contribute. Thus, clearly more work is needed to determine the role, if any, of TGR5 in the metabolic success of surgery.

The specific role of FXR in the metabolic success of surgery has also been explored. FXR-KO mice lost less weight, did not improve glucose tolerance, or shift their macronutrient preference to carbohydrates from fat in response to VSG[142]. Interestingly, the FXR KO mice preserved their postprandial GLP-1 response to surgery suggesting that FXR does not regulate GLP-1 secretion but also that GLP-1 secretion alone, cannot overcome the impact of loss of FXR on surgical outcome.

Downstream of FXR signaling within the liver is the small heterodimer partner (SHP) pathway. Using a viral knock-down of this pathway, Myronovych et al.[109] found that while VSG induced weight loss, there was a proinflammatory phenotype in these animals suggesting that VSG-induced improvements in hepatic lipid levels and inflammation is dependent upon SHP. Given the wide impact and multi-target organ impact of FXR and FGF15/19 signaling on metabolism, more mechanistic preclinical work is needed to understand the full impact of this system on the success of bariatric surgery.

The role of the microbiome

A potential critical factor in integrating BA processing and FXR signaling is the microbiome. FXR indirectly regulates the microbiome by regulating BA synthesis. Conversely, as discussed above, the microbiome regulates the conversion of primary BA to secondary BA within the lumen of the intestine. However, recent work suggests

that FXR also directly regulates the composition of the microbiome[143]. In turn, the microbiome regulates hepatic cholesterol 7 alpha-hydroxylase (CYP7A1; the rate limiting enzyme in BA synthesis) and FGF15 in the ileum; an effect that is dependent upon FXR signaling[144]. Clearly these data highlight the very close symbiotic relationship between FXR signaling, the microbiome, and BA.

In both WT and FXR-KO mice, the expected shift in bacteroides genus to the firmicutes genus in the microbiome was seen after VSG suggesting that these flora change in an FXR-independent manner[142]. However, the improvement in glucose homeostasis with VSG was associated with increases in a specific genus, roseburia, a butyrate producing bacterium, and this effect was not seen in FXR-KO mice. Still whether the changes in the microbiome with bariatric surgery drive the metabolic impact of surgery remains to be seen. A recent manuscript by Aron-Wisnewski et al.[145] found that severe obesity is associated with low microbial gene richness. However, RYGB patients retained this low microbial gene richness despite weight loss and cardiometabolic improvements; even in a cohort that was studied 5 years after RYGB. These data dissociate microbial dysbiosis to metabolism and also underscore that we are only at the beginning of our understanding of the impact of the microbiome on physiological regulation of body mass and certainly in the metabolic impact of bariatric surgery.

Conclusions

A simple Pubmed search for “bariatric surgery” reveals over 28,000 papers that have been published since the 1940’s when the first bariatric surgeries were performed. Most of what has been learned from this extensive literature is that bariatric surgery has widespread physiological impact. This particular review has summarized some of the work that has explored the role of the CNS, the gut, and the gut-brain axis on the responses to bariatric surgery (summarized in Figure 1). However, there is still lack an understanding of the mechanisms that underlie the success of surgery. The most promising link in mice seems to be between BA and/or FXR signaling, yet clearly more work is needed to understand the link between BA signaling and the metabolic success of surgery in humans.

Conflict of interest DAS has received research support from Novo Nordisk, Zafgen, and MedImmune. DAS has been a paid speaker for Novo Nordisk.

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med*. 2012;366:1567–76.
2. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes. *N Engl J Med*. 2017;376:641–651.
3. Welbourn R, Hollyman M, Kinsman R, et al. Bariatric Surgery Worldwide: Baseline Demographic Description and One-Year Outcomes from the Fourth IFSO Global Registry Report 2018. *Obes Surg*. Epub ahead of print 12 November 2018. DOI: 10.1007/s11695-018-3593-1.
4. American Society for Metabolic and Bariatric Surgery. Estimate of Bariatric Surgery Numbers, 2011-2016 | American Society for Metabolic and Bariatric Surgery, https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers (accessed 23 May 2018).
5. Dimick JB, Nicholas LH, Ryan AM, et al. Bariatric surgery complications before vs after implementation of a national policy restricting coverage to centers of excellence. *JAMA*. 2013;309:792–9.
6. Stefater M a, Pérez-Tilve D, Chambers AP, et al. Sleeve gastrectomy induces loss of weight and fat mass in obese rats, but does not affect leptin sensitivity. *Gastroenterology*. 2010;138:2426–36, 2436.e1–3.
7. Grayson BE, Schneider KM, Woods SC, et al. Improved rodent maternal metabolism but reduced intrauterine growth after vertical sleeve gastrectomy. *Sci Transl Med*. 2013;5:199ra112.

8. Chambers AP, Wilson-Perez HE, McGrath S, et al. The Effect of Vertical Sleeve Gastrectomy on Food Selection and Satiation in Rat. *Am J Physiol Endocrinol Metab*. Epub ahead of print 28 August 2012. DOI: 10.1152/ajpendo.00211.2012.
9. Wilson-Pérez HE, Chambers AP, Sandoval DA, et al. The effect of vertical sleeve gastrectomy on food choice in rats. *Int J Obes*. 2012;37:288–95.
10. Dirksen C, Damgaard M, Bojsen-Møller KN, et al. Fast pouch emptying, delayed small intestinal transit, and exaggerated gut hormone responses after Roux-en-Y gastric bypass. *Neurogastroenterol Motil*. 2013;25:346-e255.
11. Melissas J, Daskalakis M, Koukouraki S, et al. Sleeve gastrectomy-a 'food limiting' operation. *Obes Surg*. 2008;18:1251–6.
12. Chambers AP, Smith EP, Begg DP, et al. Regulation of gastric emptying rate and its role in nutrient-induced GLP-1 secretion in rats after vertical sleeve gastrectomy. *Am J Physiol Endocrinol Metab*. 2014;306:E424-32.
13. Stefater MA, Perez-Tilve D, Chambers AP, et al. Sleeve gastrectomy induces loss of weight and fat mass in obese rats, but does not affect leptin sensitivity. *Gastroenterology*. 2010;138:2426–36, 2436 e1–3.
14. Carey D, Pliego G, Raymond R. Body Composition and Metabolic Changes following Bariatric Surgery: Effects on Fat Mass, Lean Mass and Basal Metabolic Rate: Six Months to One-Year Follow-up. *Obes Surg*. 2006;16:1602–1608.
15. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004;351:2683–2693.
16. Hao Z, Mumphrey MB, Townsend RL, et al. Body Composition, Food Intake, and Energy Expenditure in a Murine Model of Roux-en-Y Gastric Bypass Surgery. *Obes Surg*. 2016;26:2173–2182.
17. Feng Y, Zhong C, Niu J, et al. Effects of sleeve gastrectomy on lipid and energy metabolism in ZDF rats via PI3K/AKT pathway. *Am J Transl Res*. 2018;10:3713–3722.
18. Bosy-Westphal A, Braun W, Schautz B, et al. Issues in characterizing resting energy expenditure in obesity and after weight loss. *Front Physiol*. 2013;4:47.
19. Guida B, Cataldi M, Busetto L, et al. Predictors of fat-free mass loss 1 year after

laparoscopic sleeve gastrectomy. *J Endocrinol Invest*. 2018;41:1307–1315.
20. Das SK, Roberts SB, McCrory MA, et al. Long-term changes in energy expenditure and body composition after massive weight loss induced by gastric bypass surgery. *Am J Clin Nutr*. 2003;78:22–30.
21. Carey D, Pliego G, Raymond R. Body Composition and Metabolic Changes following Bariatric Surgery: Effects on Fat Mass, Lean Mass and Basal Metabolic Rate: Six Months to One-Year Follow-up. *Obes Surg*. 2006;16:1602–1608.
22. Sjölund K, Sandén G, Håkanson R, et al. Endocrine cells in human intestine: an immunocytochemical study. *Gastroenterology*. 1983;85:1120–30.
23. Egerod KL, Engelstoft MS, Grunddal K V., et al. A Major Lineage of Enteroendocrine Cells Coexpress CCK, Secretin, GIP, GLP-1, PYY, and Neurotensin but Not Somatostatin. *Endocrinology*. 2012;153:5782–5795.
24. Grunddal K V., Ratner CF, Svendsen B, et al. Neurotensin Is Coexpressed, Coreleased, and Acts Together With GLP-1 and PYY in Enteroendocrine Control of Metabolism. *Endocrinology*. 2016;157:176–194.
25. Sykaras AG, Demenis C, Cheng L, et al. Duodenal CCK Cells from Male Mice Express Multiple Hormones Including Ghrelin. *Endocrinology*. 2014;155:3339–3351.
26. Little TJ, Doran S, Meyer JH, et al. The release of GLP-1 and ghrelin, but not GIP and CCK, by glucose is dependent upon the length of small intestine exposed. *Am J Physiol - Endocrinol Metab*;291.
27. Psichas A, Reimann F, Gribble FM, et al. Gut chemosensing mechanisms. *J Clin Invest*. 2015;125:908–917.
28. Moss CE, Glass LL, Diakogiannaki E, et al. Lipid derivatives activate GPR119 and trigger GLP-1 secretion in primary murine L-cells. *Peptides*. 2016;77:16–20.
29. Reimann F, Tolhurst G, Gribble FM. G-Protein-Coupled Receptors in Intestinal Chemosensation. *Cell Metab*. 2012;15:421–431.
30. Wren AM, Small CJ, Abbott CR, et al. Ghrelin causes hyperphagia and obesity in rats. *Diabetes*. 2001;50:2540–7.
31. Casajoana A, Pujol J, Garcia A, et al. Predictive Value of Gut Peptides in T2D Remission: Randomized Controlled Trial Comparing Metabolic Gastric Bypass,

Sleeve Gastrectomy and Greater Curvature Plication. *Obes Surg*. Epub ahead of print 27 April 2017. DOI: 10.1007/s11695-017-2669-7.

32. Nosso G, Griffo E, Cotugno M, et al. Comparative Effects of Roux-en-Y Gastric Bypass and Sleeve Gastrectomy on Glucose Homeostasis and Incretin Hormones in Obese Type 2 Diabetic Patients: A One-Year Prospective Study. *Horm Metab Res*. 2016;48:312–7.
33. Stefater MA, Sandoval DA, Chambers AP, et al. Sleeve gastrectomy in rats improves postprandial lipid clearance by reducing intestinal triglyceride secretion. *Gastroenterology*. 2011;141:939–949 e4.
34. Peterli R, Steinert RE, Woelnerhanssen B, et al. Metabolic and Hormonal Changes After Laparoscopic Roux-en-Y Gastric Bypass and Sleeve Gastrectomy: a Randomized, Prospective Trial. *Obes Surg*. Epub ahead of print 22 February 2012. DOI: 10.1007/s11695-012-0622-3.
35. Lee W-J, Chen C-Y, Chong K, et al. Changes in postprandial gut hormones after metabolic surgery: a comparison of gastric bypass and sleeve gastrectomy. *Surg Obes Relat Dis*. 2011;7:683–90.
36. Hajnal A, Kovacs P, Ahmed T, et al. Gastric bypass surgery alters behavioral and neural taste functions for sweet taste in obese rats. *Am J Physiol Gastrointest Liver Physiol*. 2010;299:G967-79.
37. Korner J, Inabnet W, Conwell IM, et al. Differential effects of gastric bypass and banding on circulating gut hormone and leptin levels. *Obes (Silver Spring)*. 2006;14:1553–1561.
38. Laferrere B, Swerdlow N, Bawa B, et al. Rise of oxyntomodulin in response to oral glucose after gastric bypass surgery in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2010;95:4072–4076.
39. Yousseif A, Emmanuel J, Karra E, et al. Differential Effects of Laparoscopic Sleeve Gastrectomy and Laparoscopic Gastric Bypass on Appetite, Circulating Acyl-ghrelin, Peptide YY3-36 and Active GLP-1 Levels in Non-diabetic Humans. *Obes Surg*. 2014;24:241–252.
40. Shin AC, Zheng H, Townsend RL, et al. Meal-induced hormone responses in a rat model of Roux-en-Y gastric bypass surgery. *Endocrinology*. 2010;151:1588–

1597.
41. Nannipieri M, Baldi S, Mari A, et al. Roux-en-Y gastric bypass and sleeve gastrectomy: mechanisms of diabetes remission and role of gut hormones. *J Clin Endocrinol Metab*. 2013;98:4391–9.
42. Chandarana K, Gelegen C, Karra E, et al. Diet and gastrointestinal bypass-induced weight loss: the roles of ghrelin and peptide YY. *Diabetes*. 2011;60:810–8.
43. Chambers AP, Jessen L, Ryan KK, et al. Weight-independent changes in blood glucose homeostasis after gastric bypass or vertical sleeve gastrectomy in rats. *Gastroenterology*. 2011;141:950–958.
44. Falken Y, Hellstrom PM, Holst JJ, et al. Changes in glucose homeostasis after Roux-en-Y gastric bypass surgery for obesity at day three, two months, and one year after surgery: role of gut peptides. *J Clin Endocrinol Metab*. 2011;96:2227–2235.
45. Laferrere B, Teixeira J, McGinty J, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2008;93:2479–2485.
46. Jorgensen NB, Jacobsen SH, Dirksen C, et al. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. *AJP Endocrinol Metab*. 2012;303:E122–E131.
47. Romero F, Nicolau J, Flores L, et al. Comparable early changes in gastrointestinal hormones after sleeve gastrectomy and Roux-En-Y gastric bypass surgery for morbidly obese type 2 diabetic subjects. *Surg Endosc*. Epub ahead of print 1 February 2012. DOI: 10.1007/s00464-012-2166-y.
48. le Roux CW, Borg C, Wallis K, et al. Gut hypertrophy after gastric bypass is associated with increased glucagon-like peptide 2 and intestinal crypt cell proliferation. *Ann Surg*. 2010;252:50–6.
49. Patel A, Yusta B, Matthews D, et al. GLP-2 receptor signaling controls circulating bile acid levels but not glucose homeostasis in Gcgr-/- mice and is dispensable for the metabolic benefits ensuing after vertical sleeve gastrectomy. *Mol Metab*.

2018;16:45–54.
50. Cheeseman CI. Upregulation of SGLT-1 transport activity in rat jejunum induced by GLP-2 infusion in vivo. *Am J Physiol*. 1997;273:R1965-71.
51. Svane MS, Jørgensen NB, Bojsen-Møller KN, et al. Peptide YY and glucagon-like peptide-1 contribute to decreased food intake after Roux-en-Y gastric bypass surgery. *Int J Obes*. 2016;40:1699–1706.
52. Tharakan G, Behary P, Wewer Albrechtsen NJ, et al. Roles of increased glycaemic variability, GLP-1 and glucagon in hypoglycaemia after Roux-en-Y gastric bypass. *Eur J Endocrinol*. 2017;177:455–464.
53. Wewer Albrechtsen NJ, Hartmann B, Veedfald S, et al. Hyperglucagonaemia analysed by glucagon sandwich ELISA: nonspecific interference or truly elevated levels? *Diabetologia*. 2014;57:1919–1926.
54. Salehi, M., Gastaldelli, A., D'Alessio DA. Altered islet function and insulin clearance cause hyperinsulinemia in gastric bypass patients with symptoms of postprandial hypoglycemia. *J Clin Endocrinol Metab*;Epub 2014.
55. Goldfine AB, Mun EC, Devine E, et al. Patients with Neuroglycopenia after Gastric Bypass Surgery Have Exaggerated Incretin and Insulin Secretory Responses to a Mixed Meal. *J Clin Endocrinol Metab*. 2007;92:4678–4685.
56. Roberts GP, Kay RG, Howard J, et al. Gastrectomy with Roux-en-Y reconstruction as a lean model of bariatric surgery. *Surg Obes Relat Dis*. Epub ahead of print 3 February 2018. DOI: 10.1016/j.soard.2018.01.039.
57. McIntyre N, Holsworth DC, Turner DS. New interpretation of oral glucose tolerance. *Lancet*. 1964;2:20–21.
58. Nauck MA, Bartels E, Orskov C, et al. Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-(7-36) amide infused at near-physiological insulinotropic hormone and glucose concentrations. *J Clin Endocrinol Metab*. 1993;76:912–7.
59. Vilsbøll T, Krarup T, Madsbad S, et al. Both GLP-1 and GIP are insulinotropic at basal and postprandial glucose levels and contribute nearly equally to the incretin effect of a meal in healthy subjects. *Regul Pept*. 2003;114:115–21.
60. Nauck M, Stöckmann F, Ebert R, et al. Reduced incretin effect in type 2 (non-

insulin-dependent) diabetes. *Diabetologia*. 1986;29:46–52.
61. Nauck MA, Kind J, K??the LD, et al. Quantification of the contribution of GLP-1 to mediating insulinotropic effects of DPP-4 inhibition with vildagliptin in healthy subjects and patients with type 2 diabetes using exendin [9-39] as a GLP-1 receptor antagonist. *Diabetes*. 2016;65:2440–2447.
62. Hansotia T, Baggio LL, Delmeire D, et al. Double incretin receptor knockout (DIRKO) mice reveal an essential role for the enteroinsular axis in transducing the glucoregulatory actions of DPP-IV inhibitors. *Diabetes*. 2004;53:1326–35.
63. Svane MS, Bojsen-Møller KN, Nielsen S, et al. Effects of endogenous GLP-1 and GIP on glucose tolerance after Roux-en-Y gastric bypass surgery. *Am J Physiol Endocrinol Metab*. 2016;310:E505-14.
64. Jacobsen SH, Olesen SC, Dirksen C, et al. Changes in gastrointestinal hormone responses, insulin sensitivity, and beta-cell function within 2 weeks after gastric bypass in non-diabetic subjects. *Obes Surg*. 2012;22:1084–96.
65. Korner J, Bessler M, Inabnet W, et al. Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. *Surg Obes Relat Dis*. 2007;3:597–601.
66. Aung L, Lee W-J, Chen SC, et al. Bariatric Surgery for Patients With Early-Onset vs Late-Onset Type 2 Diabetes. *doi.org*. 2016;151:798.
67. Jiménez A, Mari A, Casamitjana R, et al. GLP-1 and Glucose Tolerance After Sleeve Gastrectomy in Morbidly Obese Subjects with Type 2 Diabetes. *Diabetes*. 2014;63:3372–7.
68. Jørgensen NB, Dirksen C, Bojsen-Møller KN, et al. Exaggerated glucagon-like peptide 1 response is important for improved β-cell function and glucose tolerance after Roux-en-Y gastric bypass in patients with type 2 diabetes. *Diabetes*. 2013;62:3044–52.
69. Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. *Diabetes*. 2011;60:2308–14.
70. Jiménez A, Ceriello A, Casamitjana R, et al. Remission of type 2 diabetes after

Roux-en-Y gastric bypass or sleeve gastrectomy is associated with a distinct glycemic profile. *Ann Surg*. 2015;261:316–22.

71. Mokadem M, Zechner JF, Margolskee RF, et al. Effects of Roux-en-Y gastric bypass on energy and glucose homeostasis are preserved in two mouse models of functional glucagon-like peptide-1 deficiency. *Mol Metab*. 2014;3:191–201.
72. Wilson-Pérez HE, Chambers AP, Ryan KK, et al. Vertical Sleeve Gastrectomy is Effective in Two Genetic Mouse Models of Glucagon-like Peptide-1 Receptor Deficiency. *Diabetes*. 2013;62:2380–5.
73. Ye J, Hao Z, Mumphrey MB, et al. GLP-1 receptor signaling is not required for reduced body weight after RYGB in rodents. *Am J Physiol Regul Integr Comp Physiol*. 2014;306:R352-62.
74. Garibay D, McGavigan AK, Lee SA, et al. β-Cell Glucagon-Like Peptide-1 Receptor Contributes to Improved Glucose Tolerance After Vertical Sleeve Gastrectomy. *Endocrinology*. 2016;157:3405–3409.
75. Douros JD, Lewis AG, Smith EP, et al. Enhanced Glucose Control Following Vertical Sleeve Gastrectomy Does Not Require a β-Cell Glucagon-Like Peptide 1 Receptor. *Diabetes*. 2018;67:1504–1511.
76. Larraufie P, Roberts GP, McGavigan AK, et al. Important Role of the GLP-1 Axis for Glucose Homeostasis after Bariatric Surgery. *Cell Rep*. 2019;26:1399–1408.e6.
77. DeVries JH. Glucose variability: where it is important and how to measure it. *Diabetes*. 2013;62:1405–8.
78. Jiménez A, Casamitjana R, Viaplana-Masclans J, et al. GLP-1 action and glucose tolerance in subjects with remission of type 2 diabetes after gastric bypass surgery. *Diabetes Care*. 2013;36:2062–9.
79. Bobbioni-Harsch E, Huber O, Morel P, et al. Factors influencing energy intake and body weight loss after gastric bypass. *Eur J Clin Nutr*. 2002;56:551–556.
80. Dias MCG, Ribeiro AG, Scabim VM, et al. Dietary intake of female bariatric patients after anti-obesity gastroplasty. *Clinics (Sao Paulo)*. 2006;61:93–8.
81. Wardé-Kamar J, Rogers M, Flancbaum L, et al. Calorie intake and meal patterns up to 4 years after Roux-en-Y gastric bypass surgery. *Obes Surg*. 2004;14:1070–

9.
82. Moize V, Geliebter A, Gluck ME, et al. Obese patients have inadequate protein intake related to protein intolerance up to 1 year following Roux-en-Y gastric bypass. *Obes Surg*. 2003;13:23–8.
83. Trostler N, Mann A, Zilberbush N, et al. Nutrient Intake following Vertical Banded Gastroplasty or Gastric Bypass. *Obes Surg*. 1995;5:403–410.
84. Näslund I, Järnmark I, Andersson H. Dietary intake before and after gastric bypass and gastroplasty for morbid obesity in women. *Int J Obes*. 1988;12:503–13.
85. Brolin RE, Robertson LB, Kenler HA, et al. Weight loss and dietary intake after vertical banded gastroplasty and Roux-en-Y gastric bypass. *Ann Surg*. 1994;220:782–90.
86. Shin AC, Zheng H, Pistell PJ, et al. Roux-en-Y gastric bypass surgery changes food reward in rats. *Int J Obes*.
87. Zheng H, Shin AC, Lenard NR, et al. Meal patterns, satiety, and food choice in a rat model of Roux-en-Y gastric bypass surgery. *Am J Physiol Regul Integr Comp Physiol*. 2009;297:R1273-1282.
88. Mathes CM, Bohnenkamp RA, Blonde GD, et al. Gastric bypass in rats does not decrease appetitive behavior towards sweet or fatty fluids despite blunting preferential intake of sugar and fat. *Physiol Behav*. 2015;142:179–88.
89. Ullrich J, Ernst B, Wilms B, et al. Roux-en Y Gastric Bypass Surgery Reduces Hedonic Hunger and Improves Dietary Habits in Severely Obese Subjects. *Obes Surg*. 2013;23:50–55.
90. Makaronidis JM, Neilson S, Cheung W-H, et al. Reported appetite, taste and smell changes following Roux-en-Y gastric bypass and sleeve gastrectomy: Effect of gender, type 2 diabetes and relationship to post-operative weight loss. *Appetite*. 2016;107:93–105.
91. Zerrweck C, Zurita L, Álvarez G, et al. Taste and Olfactory Changes Following Laparoscopic Gastric Bypass and Sleeve Gastrectomy. *Obes Surg*. 2016;26:1296–1302.
92. le Roux CW, Bueter M, Theis N, et al. Gastric bypass reduces fat intake and

preference. *AJP Regul Integr Comp Physiol*. 2011;301:R1057–R1066.
93. Boxwell AJ, Chen Z, Mathes CM, et al. Effects of high-fat diet and gastric bypass on neurons in the caudal solitary nucleus. *Physiol Behav*. 2015;152:329–39.
94. Hunt KF, Dunn JT, le Roux CW, et al. Differences in Regional Brain Responses to Food Ingestion After Roux-en-Y Gastric Bypass and the Role of Gut Peptides: A Neuroimaging Study. *Diabetes Care*. 2016;39:1787–1795.
95. Halperin F, Patti ME, Skow M, et al. Continuous glucose monitoring for evaluation of glycemic excursions after gastric bypass. *J Obes*. 2011;2011:869536.
96. Shin AC, Zheng H, Berthoud H-R. Vagal innervation of the hepatic portal vein and liver is not necessary for Roux-en-Y gastric bypass surgery-induced hypophagia, weight loss, and hypermetabolism. *Ann Surg*. 2012;255:294–301.
97. Hankir MK, Seyfried F, Hintschich CA, et al. Gastric Bypass Surgery Recruits a Gut PPAR-α-Striatal D1R Pathway to Reduce Fat Appetite in Obese Rats. *Cell Metab*. Epub ahead of print 2 January 2017. DOI: 10.1016/j.cmet.2016.12.006.
98. Bueter M, Löwenstein C, Ashrafian H, et al. Vagal sparing surgical technique but not stoma size affects body weight loss in rodent model of gastric bypass. *Obes Surg*. 2010;20:616–22.
99. Hao Z, Townsend RL, Mumphrey MB, et al. Vagal Innervation of Intestine Contributes to Weight Loss After Roux-en-Y Gastric Bypass Surgery in Rats. *Obes Surg*. Epub ahead of print 28 July 2014. DOI: 10.1007/s11695-014-1338-3.
100. Mansuy-Aubert V, Gautron L, Lee S, et al. Loss of the liver X receptor LXRα/β in peripheral sensory neurons modifies energy expenditure. *Elife*;4. Epub ahead of print 15 June 2015. DOI: 10.7554/eLife.06667.
101. Liu C, Bookout AL, Lee S, et al. PPARγ in Vagal Neurons Regulates High-Fat Diet Induced Thermogenesis. *Cell Metab*. 2014;19:722–730.
102. Williams EK, Chang RB, Strochlic DE, et al. Sensory Neurons that Detect Stretch and Nutrients in the Digestive System. *Cell*. 2016;166:209–221.
103. Dailey MJ. Nutrient-induced intestinal adaption and its effect in obesity. *Physiol Behav*. 2014;136:74–78.
104. Mumphrey MB, Hao Z, Townsend RL, et al. Sleeve Gastrectomy Does Not Cause Hypertrophy and Reprogramming of Intestinal Glucose Metabolism in Rats. *Obes*

Surg. 2015;25:1468–73.

105. Mumphrey MB, Patterson LM, Zheng H, et al. Roux-en-Y gastric bypass surgery increases number but not density of CCK-, GLP-1-, 5-HT-, and neurotensin-expressing enteroendocrine cells in rats. *Neurogastroenterol Motil*. 2013;25:e70-9.
106. Hansen CF, Bueter M, Theis N, et al. Hypertrophy dependent doubling of L-cells in Roux-en-Y gastric bypass operated rats. *PLoS One*. 2013;8:e65696.
107. Nguyen NQ, Debreceni TL, Bambrick JE, et al. Rapid gastric and intestinal transit is a major determinant of changes in blood glucose, intestinal hormones, glucose absorption, and postprandial symptoms after gastric bypass. *Obesity (Silver Spring)*. 2014;22:2003–9.
108. Cavin J-B, Couvelard A, Lebtahi R, et al. Differences in Alimentary Glucose Absorption and Intestinal Disposal of Blood Glucose Following Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy. *Gastroenterology*. Epub ahead of print 16 October 2015. DOI: 10.1053/j.gastro.2015.10.009.
109. Myronovych A, Salazar-Gonzalez R-M, Ryan KK, et al. The role of small heterodimer partner in nonalcoholic fatty liver disease improvement after sleeve gastrectomy in mice. *Obesity*. 2014;22:2301–2311.
110. Nausheen S, Shah IH, Pezeshki A, et al. Effects of sleeve gastrectomy and ileal transposition, alone and in combination, on food intake, body weight, gut hormones, and glucose metabolism in rats. *AJP Endocrinol Metab*. 2013;305:E507–E518.
111. Haeusler RA, Astiarraga B, Camastra S, et al. Human insulin resistance is associated with increased plasma levels of 12α-hydroxylated bile acids. *Diabetes*. 2013;62:4184–91.
112. Wewalka M, Patti M-E, Barbato C, et al. Fasting Serum Taurine-Conjugated Bile Acids Are Elevated in Type 2 Diabetes and Do Not Change With Intensification of Insulin. *J Clin Endocrinol Metab*. 2014;99:1442–1451.
113. Sonne DP, van Nierop FS, Kulik W, et al. Postprandial Plasma Concentrations of Individual Bile Acids and FGF-19 in Patients With Type 2 Diabetes. *J Clin Endocrinol Metab*. 2016;101:3002–9.

114. Patti M-E, Houten SM, Bianco AC, et al. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. *Obesity (Silver Spring)*. 2009;17:1671–7.
115. Kohli R, Bradley D, Setchell KD, et al. Weight Loss Induced by Roux-en-Y Gastric Bypass But Not Laparoscopic Adjustable Gastric Banding Increases Circulating Bile Acids. *J Clin Endocrinol Metab*. 2013;98:E708-12.
116. Patti ME, Houten SM, Bianco AC, et al. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. *Obes (Silver Spring)*. 2009;17:1671–1677.
117. Pournaras DJ, Glicksman C, Vincent RP, et al. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. *Endocrinology*. 2012;153:3613–9.
118. Sachdev S, Wang Q, Billington C, et al. FGF 19 and Bile Acids Increase Following Roux-en-Y Gastric Bypass but Not After Medical Management in Patients with Type 2 Diabetes. *Obes Surg*. 2016;26:957–965.
119. Steinert RE, Peterli R, Keller S, et al. Bile acids and gut peptide secretion after bariatric surgery: a 1-year prospective randomized pilot trial. *Obesity (Silver Spring)*. 2013;21:E660-8.
120. Yu H, Ni Y, Bao Y, et al. Chenodeoxycholic Acid as a Potential Prognostic Marker for Roux-en-Y Gastric Bypass in Chinese Obese Patients. *J Clin Endocrinol Metab*. 2015;100:4222–30.
121. Ryan KK, Tremaroli V, Clemmensen C, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature*. 2014;509:183–8.
122. Myronovych A, Kirby M, Ryan KK, et al. Vertical sleeve gastrectomy reduces hepatic steatosis while increasing serum bile acids in a weight-loss-independent manner. *Obes (Silver Spring)*. 2014;22:390–400.
123. Ozcan U, Yilmaz E, Ozcan L, et al. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science*. 2006;313:1137–40.
124. Nielsen S, Svane MS, Kuhre RE, et al. Chenodeoxycholic acid stimulates glucagon-like peptide-1 secretion in patients after Roux-en-Y gastric bypass.

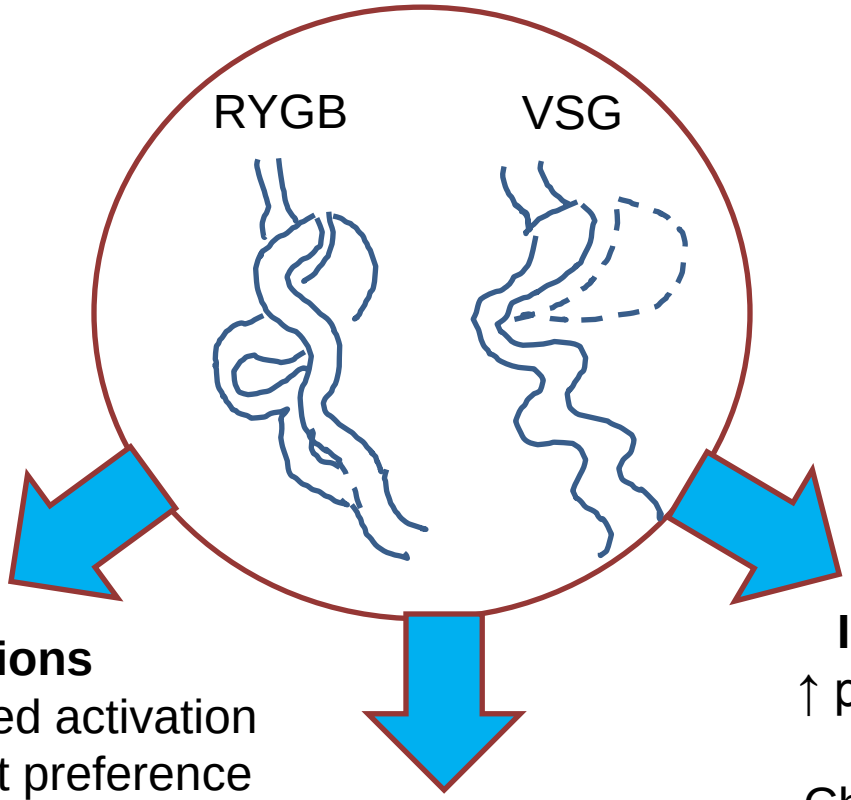
Physiol Rep. 2017;5:e13140.

125. Kawamata Y, Fujii R, Hosoya M, et al. A G protein-coupled receptor responsive to bile acids. *J Biol Chem*. 2003;278:9435–40.
126. Parks DJ, Blanchard SG, Bledsoe RK, et al. Bile acids: natural ligands for an orphan nuclear receptor. *Science (80-)*. 1999;284:1365–1368.
127. Makishima M, Okamoto AY, Repa JJ, et al. Identification of a nuclear receptor for bile acids. *Science*. 1999;284:1362–5.
128. Katsuma S, Hirasawa A, Tsujimoto G. Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. *Biochem Biophys Res Commun*. 2005;329:386–390.
129. Watanabe M, Houten SM, Mataki C, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature*. 2006;439:484–489.
130. Cariou B, van Harmelen K, Duran-Sandoval D, et al. The farnesoid X receptor modulates adiposity and peripheral insulin sensitivity in mice. *J Biol Chem*. 2006;281:11039–49.
131. Cipriani S, Mencarelli A, Palladino G, et al. FXR activation reverses insulin resistance and lipid abnormalities and protects against liver steatosis in Zucker (*fa* / *fa*) obese rats. *J Lipid Res*. 2010;51:771–784.
132. Ma K, Saha PK, Chan L, et al. Farnesoid X receptor is essential for normal glucose homeostasis. *J Clin Invest*. 2006;116:1102–1109.
133. Morton GJ, Matsen ME, Bracy DP, et al. FGF19 action in the brain induces insulin-independent glucose lowering. *J Clin Invest*. 2013;123:4799–808.
134. Fu L, John LM, Adams SH, et al. Fibroblast growth factor 19 increases metabolic rate and reverses dietary and leptin-deficient diabetes. *Endocrinology*. 2004;145:2594–603.
135. Kir S, Beddow SA, Samuel VT, et al. FGF19 as a Postprandial, Insulin-Independent Activator of Hepatic Protein and Glycogen Synthesis. *Science (80-)*. 2011;331:1621–1624.
136. Nies VJM, Sancar G, Liu W, et al. Fibroblast Growth Factor Signaling in Metabolic Regulation. *Front Endocrinol (Lausanne)*. 2016;6:193.
137. Gerhard GS, Styer AM, Wood GC, et al. A role for fibroblast growth factor 19 and

bile acids in diabetes remission after Roux-en-Y gastric bypass. *Diabetes Care*. 2013;36:1859–64.

138. Pournaras DJ, Glicksman C, Vincent RP, et al. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. *Endocrinology*. 2012;153:3613–9.
139. McGavigan AK, Garibay D, Henseler ZM, et al. TGR5 contributes to glucoregulatory improvements after vertical sleeve gastrectomy in mice. *Gut*. Epub ahead of print 28 October 2015. DOI: 10.1136/gutjnl-2015-309871.
140. Ding L, Sousa KM, Jin L, et al. Vertical sleeve gastrectomy activates GPBAR-1/TGR5 to sustain weight loss, improve fatty liver, and remit insulin resistance in mice. *Hepatology*. 2016;64:760–773.
141. Vassileva G, Golovko A, Markowitz L, et al. Targeted deletion of Gpbar1 protects mice from cholesterol gallstone formation. *Biochem J*. 2006;398:423–30.
142. Ryan KK, Tremaroli V, Clemmensen C, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature*. 2014;509:183–188.
143. Parséus A, Sommer N, Sommer F, et al. Microbiota-induced obesity requires farnesoid X receptor. *Gut*. 2017;66:429–437.
144. Sayin SI, Wahlström A, Felin J, et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metab*. 2013;17:225–35.
145. Aron-Wisnewsky J, Prifti E, Belda E, et al. Major microbiota dysbiosis in severe obesity: fate after bariatric surgery. *Gut*. 2018;gutjnl-2018-316103.

Figure 1. The impact of VSG and RYGB on CNS, gut, and the gut-brain axis. The CNS is more highly activated by surgery and induces changes in feeding patterns and macronutrient preference. The gut responds with increases postprandial peptide secretions, increases in plasma bile acids (BA) and changes in the microbiome. The gut-brain axis may integrate these two systems as celiac gangliectomy blunts weight loss responses to RYGB.



CNS adaptations
↑ CNS nutrient-induced activation
Altered macronutrient preference
Altered feeding patterns

Gut-brain axis integration
Celiac ganglion necessary for surgery-induced weight loss

Intestinal adaptations
↑ postprandial gut peptides
↑bile acids
Change in the microbiome