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REVIEW ARTICLE

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Neuroendocrine mechanisms underlying bariatric surgery: Insights from human studies and animal models

A. Stefanidis[1] | B. J. Oldfield[2]

[1]Department of Physiology, Monash University, Clayton, VIC, Australia

[2]Metabolic Disease and Obesity Program, Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia

Correspondence
Brian Oldfield, Department of Physiology, Monash University, Clayton, VIC, Australia.
Email: brian.oldfield@monash.edu

Obesity has reached epidemic proportions and, to date, bariatric surgery remains the only effective treatment for morbid obesity in terms of its capacity to achieve durable weight loss. Bariatric surgery procedures, including Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB) and sleeve gastrectomy (SG), have been the primary procedures conducted over the past decade, with SG increasing in popularity over the past 5 years at the expense of both RYGB and AGB. Although these procedures were initially proposed to function via restrictive or malabsorptive mechanisms, it is now clear that profound physiological changes underlie the metabolic improvements in patients who undergo bariatric surgery. Data generated in human patients and animal models highlight the rapid and sustained changes in gut hormones that coincide with these procedures. Furthermore, recent studies highlight the involvement of the nervous system, specifically the vagus nerve, in mediating the reduction in appetite and food intake following bariatric surgery. What is unclear is where these pathways converge and interact within the gut-brain axis and whether vagally-mediated circuits are sufficient to drive the metabolic sequalae following bariatric surgery.

KEYWORDS
adjustable gastric banding, bariatric surgery, Roux-en-Y gastric bypass, sleeve gastrectomy, vagus nerve

1 | INTRODUCTION

Bariatric surgery is now acknowledged as the most effective therapy for the management and treatment of obesity and its associated co-morbidities. Bariatric surgery, including Roux en Y gastric bypass (RYGB), sleeve gastrectomy (SG) and laparoscopic adjustable gastric banding (LAGB), has the capacity to achieve body weight loss of 20%-30% or excess body weight loss of 50%-70%, which has been shown to be sustained for up to 15 years.[1,2] These procedures have not only produced profound weight loss, but also have shown improvements in quality of life and a reduction in mortality and morbidity related to cardiovascular heart disease and diabetes.[3-5] By comparison, lifestyle modifications and recently approved pharmacotherapies achieve a modest weight loss of 5%-10%.[6]

2 | ROLE OF GUT HORMONES

The gastrointestinal tract is the body's largest endocrine organ and releases more than 20 different hormones that are sensitive to both gut distension and nutrient content.[7] Indeed, an evolving hypothesis for the mechanisms underlying the efficacy of bariatric surgery, particularly in relation to improvements (or resolution) of diabetes, lies in the impact of these procedures on the secretion of many of these gut hormones. This concept involves both the foregut and hindgut theories, with the former proposing that food bypassing the duodenum leads to a reduction in the release or possibly activation of a factor(s) inhibiting insulin secretion or impairing insulin sensitivity.[8,9] By contrast, the latter supports the notion that rapid transit of undigested nutrients to the distal gastrointestinal tract triggers a factor(s) enhancing insulin

secretion and/or sensitivity.[10,11] Changes in the concentrations of many gut-derived hormones, including glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), peptide YY (PYY), oxyntomodulin, cholecystokinin and ghrelin, have been consistently reported and reviewed (12,13), particularly following RYGB and SG. In view of their established roles in appetite control and glucose metabolism, these hormones are likely to mediate the positive effects of bariatric surgery on body weight and blood glucose (Figure 1).

2.1 | Hormonal changes in human patients

Following RYGB in human patients, the most substantial change in gut hormones occurs in post-prandial levels of GLP-1 and PYY, which have been reported to increase by more than 10-fold.[14,15] Changes in GLP-1 levels occur within days of the surgery and are likely to facilitate weight loss and contribute to the early improvements in glucose homeostasis given the ability of GLP-1 to increase insulin secretion, suppress glucagon release, inhibit hepatic glucose production and decrease food intake.[16,17] The importance of the exaggerated GLP-1 response in mediating the improved glucose tolerance, at least after RYGB, has been highlighted in a recent study involving pharmacological blockade of the GLP-1R after RYGB.[18] Antagonism of the GLP-1 receptor using exendin$^{9\text{-}39}$ results in a reversal of the improved beta cell glucose sensitivity and increased postprandial glucagon release, suggesting that the increased endogenous GLP-1 secretion is important for the acute effects of RYGB in patients with type 2 diabetes. Similar to GLP-1, PYY is produced by enteroendocrine L cells in the distal small intestine and colon; however, its main role appears to be in the central control of appetite and food intake.[19] Levels of PYY have been shown to increase post-prandially, which, similar to GLP-1, is evident in the immediate period post-surgery and is maintained after a year[20,21] and occurs following RYGB,[20] SG[22] and gastric banding.[23] The latter result in relation to gastric banding appears to be less robust and is difficult to reproduce in patients.[24]

Adding to this, changes in ghrelin secretion have been proposed to contribute to the reduction in food intake that occurs following bariatric surgery. Initially, ghrelin levels were reported to decrease compared to diet-induced weight loss;[25] however, subsequent studies in patients have challenged these findings, reporting reductions, no alternations and even a rise in fasting and post-prandial levels of ghrelin (26,27). Changes in ghrelin levels following SG are much more consistent with the majority of studies reporting a significant decrease in ghrelin concentrations (22,28), an effect that is likely to be attributed to the reduction in ghrelin-producing cells or possibly the absence of direct nutrient contact with the gastric mucosa. In comparison, LAGB induced weight loss has been demonstrated to cause an elevation in ghrelin levels (23,29), which would be expected to stimulate appetite and food intake.

In addition to GLP-1, PYY and ghrelin there are a number of other gut-derived hormones that are altered following bariatric surgery, the extent to which being influenced by the specific procedure. For example, GIP and cholecystokinin have been reported to increase with SG; however, changes following RYGB are somewhat variable.[21,33] Similarly, fasting neurotensin levels have been reported to decrease in RYGB patients but increase post-prandially,[34] which is at odds with previous studies[35] measuring the precursor proneurotensin. Furthermore, a number of studies have reported that, in addition to the release of GLP-1 and PYY, oxyntomodulin levels are elevated after RYGB.[14,36] Taken together, bariatric surgery is associated with a shift in the secretion of many gastrointestinal-derived hormones, which are likely to work in concert with a myriad of other factors to mediate the beneficial effects of these procedures.

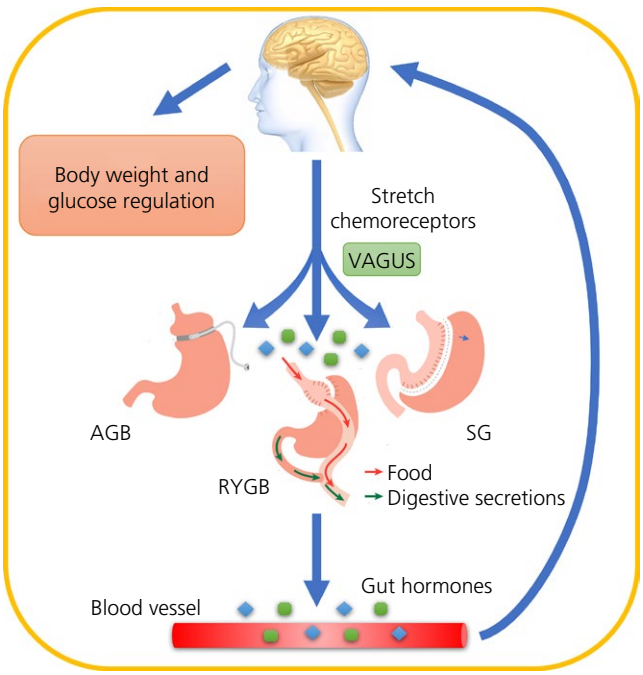

FIGURE 1 Bariatric surgery procedures, including Roux en Y gastric bypass (RYGB), sleeve gastrectomy (SG) and adjustable gastric banding (AGB), influence body weight and glucose regulation via central neural circuits that are recruited by vagally-mediated pathways following activation of stretch- or chemoreceptors in the stomach. Gut hormones are able to exert their effects on central pathways by either acting locally on vagal endings or via the circulation

2.2 | Gut hormone changes in animal models of bariatric surgery

The observations made in human patients with respect to gut hormone changes have been similarly described in rodent studies. For example, GLP-1 levels following the administration of a mixed meal increase 10-fold after RYGB and SG. Increased postprandial GLP-1 and insulin release was not a direct result of reductions in body weight and food intake following these procedures because these changes were absent in pair-fed controls. These elevations coincide with a five-fold increase in insulin levels, which are abolished following the administration of the GLP-1 antagonist, exendin.[9-39] Therefore, it was hypothesised that GLP-1 action may underlie many of the metabolic improvements following RYGB and SG.[37] However, when these surgeries are performed in mice lacking GLP-1 receptors (GLP1R KO), mice respond similarly to SG surgery in terms of reduced body weight

and adiposity, improvements in glucose homeostasis, and altered food choice. Therefore, GLP1R activity is not necessary to generate the metabolic effects of SG surgery.[38] In comparison, PYY has been shown to play a key role in mediating the early weight loss observed post gastric bypass surgery. In this respect, PYY knockout mice that undergo gastric bypass surgery lose similar amounts of weight to their sham-operated counterparts.[39]

As described earlier, no increases in postprandial GLP-1 and only sporadic elevation of circulating PYY have been reported after gastric banding in humans patients;[24,40] however, our recently published data challenge these findings where we demonstrate that the gut-derived hormones GLP-1 and PYY are significantly elevated in response to a standard caloric meal in rats with an inflated gastric band.[41] This elevation of anorexigenic hormones is in keeping with the satiety-inducing effects of the AGB and consistent with the decreased food intake observed in the rat model. The differences observed between data-derived humans and animal models are difficult to reconcile; however, it has been proposed that these may relate to technical assay issues and the extremely labile property of hindgut hormones.[23] As such, as a result of the rapid degradation of GLP-1 by DPP-4, plasma concentrations are reported to rapidly reduce to 50% in the hepatoportal vein and even further in the systemic circulation (10% or less).[42] Therefore, it is possible that local GLP-1 concentrations are altered but, because of the rapid degradation of the peptide, these are not detectable. This does not necessarily preclude the significance of GLP-1 in exerting its effects on gastric emptying, motility, food intake and blood glucose levels because GLP-1 may act in a paracrine manner on receptors located on vagal afferents[43] to activate central neural circuits.

Given the ability of ghrelin to regulate glucose metabolism through both central and peripheral actions,[30] it is not surprising that the reduction in ghrelin secretion following bariatric surgery results in rapid improvements in glucose homeostasis.[31] This is particularly relevant to SG surgery, where the majority of the ghrelin producing cells are removed. In this respect, a recent rodent study demonstrated significantly reduced ghrelin levels following SG but not following RYGB; however, the efficacy of SG was not modified in ghrelin deficient mice,[32] demonstrating that ghrelin signalling is not a critical element in determining SG mediated weight loss and improvements in glucose homeostasis.

The importance of other gut-derived hormones in mediating the reduction in food intake following bariatric surgery has been recently interrogated in a rodent model of the RYGB. For example, neurotensin, which is co-expressed with GLP-1 and PYY in certain enteroendocrine cells,[44] is increased in plasma following gastric bypass surgery, and the administration of a neurotensin receptor antagonist to RYGB rats results in a transient increase in food intake, which is not apparent in sham operated-animals, with such an effect being unlikely to involve a vagal conduit.[45]

3 | ROLE OF THE VAGUS NERVE

The neural connections between the gastrointestinal tract and the brain, specifically those traveling in the vagus nerve, are implicated in mediating weight loss following bariatric surgery. The gastrointestinal tract is innervated by motor and sensory fibres within the vagus nerve with sensory fibres ending in close proximity to ghrelin-producing cells in the gastric fundus, as well as enteroendocrine cells such as L-cells known to secrete the anorexigenic hormones GLP-1, PYY and oxyntomodulin. These and are other gut-derived hormones are able to either (i) act locally (in an autocrine fashion) on specific receptors located on vagal afferent endings, whose cells bodies reside in the nodose ganglion, and synapse on first-order neurones in the hindbrain or, alternatively, (ii) they may enter the bloodstream and activate receptors located in the brainstem or hypothalamus to exert their effects on food intake and blood glucose regulation.

3.1 | Insights from rodent studies

During bariatric surgery, particularly RYGB and SG, gastric branches of the vagus nerve are cut, creating damage to preganglionic efferent and afferent fibres.[46-48] The degree and specifics of the damage are related to the bariatric procedure because RYGB involves a transverse cut to the stomach where gastric vagal branches, very close to their origin from the oesophageal plexus,[49] are damaged. In comparison, SG involves a longitudinal cut to the stomach[50,51] and therefore only the very distal branches of the gastric vagus are compromised. In the same vein, recent data demonstrate transient withdrawal and remodelling of central vagal afferent terminals in the nucleus of the solitary tract (NTS) following subdiaphragmatic vagotomy,[52] as well as activation of microglia in the NTS, dorsal motor nucleus of the vagus nerve (DMV) and nodose ganglia, which remains significantly elevated in the nodose ganglia and DMV for at 7 weeks following vagotomy.[53] Therefore, given the defined role of the vagus in regulating gut function and relaying sensory information to feeding centres in the hindbrain, it is possible that these processes are altered following bariatric surgery.[46]

In this respect, the degree of vagal innervation of the gastrointestinal tract following RYGB has been investigated in an obese mouse model genetically expressing the reporter tdTomato in all peripheral nerves. Substantial denervation of the glandular and distal stomach was demonstrated; however, RYGB did not modify the innervation to the rest of the intestines and glucostatic organs.[54] Importantly, the preservation of vagal afferent endings during surgery is associated with enhanced and sustained body weight loss in animal models of RYGB.[55,56] By contrast, the importance of the vagus nerve in mediating hypophagia, weight loss and metabolic control following RYGB was rejected in a recent rodent study, which involved selective vagotomy to the hepatic branch of the vagus;[57] however, in that study, it was proposed that the other vagal branches innervating the small bowel were unaffected and so it is possible that these may contribute to the changes in food intake and body weight loss following RYGB. In comparison, a similar study involving retention of the hepatic branch of the vagus in a rat model of RYGB resulted in maintained weight reduction and increased GLP-1 and insulin levels in the serum, suggesting that the vagus is important in the mediating the improvements in glycaemic control following RYGB.[58]

The activation of central neural circuits, downstream of vagal afferent signalling, was recently suggested to be involved in mediating satiation and glycaemic control in a mouse model of RYGB.[59] These data

implicate the vagal endings in sensing the elevation in gastric distension and nutrients in the roux limb to activate an anorexigenic pathway involving the NTS, lateral parabrachial nucleus and central nucleus of the amygdala. The activation of this pathway in the immediate period following RYGB is likely to be responsible for the dramatic reduction in food intake after RYGB and may also contribute to the consumption of smaller and slower meals. In addition, there is evidence supporting the re-organisation of hindbrain feeding circuits following RYGB and SG. Using a retrograde tracing approach, RYGB was shown to significantly decrease the density of vagal afferents in the NTS and promote the activation of microglia within vagal structures, whereas SG resulted in the sprouting of vagal afferents synapsing in the NTS without associated inflammatory responses.[60] Furthermore, experimental models of SG indicate that vagal mechanisms contribute to the efficacy of the procedure and that there is a lower threshold for activation of neurones in the NTS in response to a nutrient stimulus, as demonstrated by elevated levels of Fos protein.[51] We have also recently generated data showing increased neural activation, under fasting conditions, within the same vagal circuits (unpublished observations; A Stefanidis, CMC Lee, BJ Oldfield). However, what is unknown is whether these effects occur in response to activation of mechanosensitive vs nutrient-sensory modalities. Furthermore, the extent to which vagal mechanisms are central to the reduction in appetite (and weight loss) induced by SG also remains unclear.

In terms of the AGB, our recently published data support the role of vagal afferents in mediating its impact on food intake and body weight.[41] Importantly, following both acute and chronic AGB inflation, there is an activation of vagal sensory endings, as demonstrated by elevated levels of Fos protein in the NTS and in the lateral parabrachial nuclei of the brainstem. Furthermore, when capsaicin (a neurotoxin that destroys unmyelinated c-fibres) is introduced at critical concentrations into the peritoneum or directly applied onto the stomach wall, there is a complete elimination of both the elevated Fos labelling in the brainstem and weight loss induced by AGB inflation, highlighting the importance of vagal sensory fibres to the efficacy of the AGB. The contribution of hormones to the effectiveness of the AGB cannot be completely ignored despite an elimination of the effect of the band after vagal lesions because gut peptides are likely to act via receptor vagal nerve endings.[61]

3.2 | Insights from human studies

Evidence supporting the role of the vagus nerve and, more specifically, its sensory components in human patients is limited. In this respect, the pressure generated in the proximal alimentary limb of the RYGB following gradual balloon inflation has been shown to predict meal size as early as 6 weeks after surgery and maintained in patients 1-year post RYGB-surgery.[62] It is therefore possible that the rapid entry of food from the oesophagus through the Roux limb is detected by mechanoreceptors that trigger activation of vagal pathways to ultimately drive RYGB patients to terminate food intake.

It is clear from the results of studies of banded patients with a properly adjusted band that there is an AGB- induced satiety. In a randomised, blinded, cross-over trial, patients with optimally adjusted gastric bands reported reductions in hunger following an overnight fast[29] as well as increased satiation following the consumption of a meal, supporting the notion that band-induced satiety is not mediated purely by restriction.

4 | OTHER FACTORS THAT MAY PROMOTE AN INTERACTION BETWEEN GUT HORMONES AND VAGAL PATHWAYS

There is now a growing body of evidence supporting the interaction of gut microbiota and bile acids in the regulation of energy metabolism.[63] Importantly, these factors have been implicated in the mechanisms underlying the effectiveness of bariatric surgery and are likely to exert their effects on metabolism through a complex network of communication involving the vagus nerve and neuroendocrine pathways.[64] Obese individuals display differences in the composition of gut microbiota,[65] which can be modified in response to shifts in caloric consumption and macronutrient composition.[66] Recent work demonstrates that bariatric surgery is associated with increased microbial diversity and altered microbial composition following RYGB in humans[67-70] and following SG and RYGB in rodents.[71-73] Furthermore, colonisation of germ-free mice with faecal material from mice after gastric bypass results in reduced body weight and adiposity, supporting the notion that RYGB associated gut microbiota can have direct effects on host metabolism.[71] Interestingly, a recently published human study measured the faecal microbial composition and metabolites of normal weight and morbidly obese pre-bariatric surgery patients, as well as individuals following either RYGB or LAGB. There was a substantial shift in the faecal microbiome and metabolome in patients who underwent RYGB and AGB compared to normal weight and obese participants.[74] Given the substantial anatomical differences between these two bariatric procedures, it is not surprising that the differences were more pronounced in patients undergoing gastric bypass compared to LAGB.

It is well established that the gut microbiota has a dynamic interplay with bile acid metabolism, conversion and subsequent signalling.[63] The production of bile acids is also highly regulated through the nuclear farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5), where the latter is highly expressed in enteroendocrine L cells, and, as such, upon activation, can result in the release of the anorexigenic hormones GLP-1 and PYY. As noted above, such gut-derived peptides are well positioned to exert an effect on vagal sensory endings via local GLP-1 and PYY receptors. Importantly, a recent comparative study reported that total circulating and primary bile acids are elevated following RYGB in humans, pigs and rats.[75] Indeed, a study conducted in RYGB patients showed increased post-prandial bile acid secretion, as well as increased FGF19 responses, compared to obese controls, where FGF19 is an intestinal factor that is important in the regulation of bile acids and energy metabolism through bile acid-mediated activation of FXR.[76] FXR has also been shown to be an important contributor to the weight loss and improved glucose metabolism following SG in mice.[73] Additionally, TGR5 appears to be important in the glucoregulatory benefits of SG

by promoting metabolically favourable shifts in the circulating bile acid pool.[77]

There is accumulating evidence from these and other studies supporting the necessary role of gut microbiota and bile acid-signalling in mediating the positive metabolic effects of bariatric surgery. However, what remains to be determined is the specific mechanism(s) by which microbial metabolites and bile acids regulate energy metabolism and to what extent these involve vagal pathways and the secretion of gut-derived hormones.

5 | CONCLUDING REMARKS

It is clear that the mechanisms underlying the efficacy of bariatric surgery are complex and involve changes that are simply not a result of restriction and malabsorption. Clinical observations and studies conducted in experimental models highlight a complex interplay of hormonal and neural pathways that converge and possibly interact at various levels of the gut-brain axis to regulate energy balance. A better understanding of these processes is key to the refinement and optimisation of surgical approaches and may also lead to the identification of pharmacological targets for the development of nonsurgical weight-loss interventions.

ORCID


B. J. Oldfield http://orcid.org/0000-0002-8609-6589

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