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Mechanisms of weight loss after obesity surgery

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Abstract:	Obesity surgery remains the most effective treatment for obesity and its complications. Weight loss was initially attributed to decreased energy absorption from the gut but have since been linked to reduced appetitive behaviour and potentially increased energy expenditure. Implicated mechanisms associating rearrangement of the gastrointestinal tract with these metabolic outcomes include central appetite control, release of gut peptides, change in microbiota and bile acids. However, the exact combination and timing of signals remain largely unknown. In this review, we survey recent research investigating these mechanisms, and seek to provide insights on unanswered questions over how weight loss is achieved following bariatric surgery which may eventually lead to safer, nonsurgical weight-loss interventions or combinations of medications with surgery.
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Prof Daniel J. Drucker

Editor-in-Chief

Endocrine Reviews

Dear Prof Drucker,

Thank you for the acceptance of our review with minor revisions. We are pleased to submit a revision of our invited review entitled ‘‘Mechanisms of weight loss after obesity surgery’’, addressing the minor revisions from the reviewers, by Elina Akalestou et al for consideration by *Endocrine Reviews*. We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

In this review, we survey recent research investigating the mechanisms and unanswered questions over how weight loss is achieved following bariatric surgery which may eventually lead to safer, nonsurgical weight-loss interventions or combinations of medications with surgery.

The authors have no conflict of interest to disclose. Please address all correspondence concerning this manuscript to carel.leroux@ucd.ie.

Thank you for your consideration of this manuscript.

Sincerely,

Professor Carel le Roux

Editor Comments (if applicable):
The revised manuscript has been improved. The authors have well addressed the concerns raised by the reviewers. The manuscript can be accepted with a further minor revision.

Reviewer Comments:
Reviewer 1: The revised paper of Akaleston and colleagues has been improved. The reviewer thanks the authors for their point-by-point responses to the concerns raised by all reviewers and for clarifications made in the MS. The reviewer has no concern with the current version of the MS other than requesting clarification of the **word "exendin -9" on line 464 to "exendin - (9-30)".**

E.A. Thank you for your kind feedback, this has now been clarified on page 20, line 467.

Reviewer 3: I thank the authors for their response to previous comments and suggested corrections. I now find the manuscript suitable for publication, but noted additional comments and suggested corrections below. In my opinion, the authors should further tone down increased energy expenditure as a possible mechanism for weight loss after surgery, because energy expenditure is generally found lower or unchanged during the weight loss phase. Change in body composition (i.e. higher lean vs. fat mass) after major weight loss is a possible mechanism for the relative increase in postprandial energy expenditure observed in the studies cited to support this concept.

Minor comments :

Line 352: **'This mechanismS..'**

E.A. This has now been corrected on page 19, line 427.

Lines 356 to 359 : 'Notwithstanding discrepancies between studies, there is some agreement that there is a reduction in the activation of brain areas that respond to the involved with rewarding properties to food cues (e.g. food pictures) after RYGB and VSG 39, 40.' **Replace with '… involved CUES with rewarding properties…'?**

E.A. This has now been changed on page 12, line 259-260.

Line 361: '…that underlie this observation, **as THE…'.**

E.A. This has now been changed on page 12, line 263.

Lines 471 to 476: regarding reference 62, it should be noted that absolute 24h and post-meal energy expenditure was reduced in the 6 female participants after RYGB. The reduction in energy expenditure expressed per total body mass may be caused by the larger proportional reduction in adipose tissue mass vs. lean mass 20 months after the procedure. Unfortunately, postprandial energy expenditure per lean mass was not reported, but resting energy expenditure per lean mass tended to go down after bariatric surgery (20.6 before vs. 17.2 cal/min/kg 20 months after surgery). The same comment applies to reference 64 in which the body fat loss and ratio of lean/fat mass tended to be higher in RYGB vs. VBG. The authors should acknowledge **that in humans: 1) absolute**

energy expenditure is generally found to be reduced after surgery; and 2) the increase in energy expenditure expressed per total body mass may be at least in part explained by change in body composition (i.e. increased lean to fat mass ratio).

E.A. Thank you very much for your input on this. We agree and have inserted these limitations on page 16, line 361-365.

Reviewer 4: The authors have appropriately addressed my comments

E.A. Thank you very much.

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Mechanisms of weight loss after obesity surgery

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Abstract

Obesity surgery remains the most effective treatment for obesity and its complications. Weight loss was initially attributed to decreased energy absorption from the gut but have since been linked to reduced appetitive behaviour and potentially increased energy expenditure. Implicated mechanisms associating rearrangement of the gastrointestinal tract with these metabolic outcomes include central appetite control, release of gut peptides, change in microbiota and bile acids. However, the exact combination and timing of signals remain largely unknown. In this review, we survey recent research investigating these mechanisms, and seek to provide insights on unanswered questions over how weight loss is achieved following bariatric surgery which may eventually lead to safer, nonsurgical weight-loss interventions or combinations of medications with surgery.

(117 words)

Introduction

Obesity surgery over the past six decades has been successful not only in providing a means of achieving substantial weight loss but also in giving us many novel insights on the pathophysiology of obesity. Obesity surgery was first described in the 1960s, when it was observed that patients with sub-total gastrectomy for cancer lost a considerable amount of weight [1]. Several modifications to the technique led to the first laparoscopic gastric bypass in 1994 [2], and the establishment of the three techniques most widely-used in clinical practice today.

The two main approaches that are currently performed widely are Roux-en-Y Gastric Bypass (RYGB) and Vertical Sleeve Gastrectomy (VSG). RYGB involves the creation of a small gastric pouch (~30 mL) that is anastomosed to the proximal jejunum, which has been transected at 30–75 cm from the ligament of Treitz, to form the “alimentary limb”. The continuity of the intestine is restored via a jejuno-jejunal anastomosis between the alimentary limb and the excluded biliopancreatic limb approximately 75–150 cm distal to the gastrojejunostomy [3]. As a result, food bypasses most of the stomach, the entire duodenum, and the proximal jejunum. VSG involves dividing the stomach along its vertical length to create a sleeve and removing ~75% of its volume [4]. Although decreasing in popularity, the adjustable gastric banding (AGB) involves placing a silicone ring around the proximal stomach, bellow the gastroesophageal junction. The ring pressure is adjusted through fluid injected or withdrawn from a subcutaneous port [5].

Efficacy is not the same among procedures, as RYGB and VSG cause more weight loss compared to AGB [6]. Patients benefit not only form weight loss, but more vitally

from improvements in glycaemic control [7], reduced cardiovascular morbidity and mortality [8] and reduced incidence of cancer [9]. All three procedures cause no mechanical restriction with little or no macronutrient malabsorption. Instead, weight loss is due to changes in the physiology of body weight regulation.

In this review, we will explore the biological mechanisms underpinning weight loss. . We will not discuss the mechanisms underlying glycaemic/metabolic improvements as they fall outside the already wide scope of this review. The impact of obesity surgery on metabolism appears to be predominantly because of the substantial and sustained weight loss, but given the large number of mechanisms which are not weight loss related we expect that the beneficial metabolic outcome at individual level may be a composite of the weight loss together with non-weight loss related mechanisms.

We will focus on mechanistic studies in humans and animal models focusing on RYGB, VSG and AGB, as they are the most commonly performed operations. While animal data may not always apply to humans, they also raise new questions that can be answered in humans and answer questions that cannot be answered in humans.

Mechanisms underlying weight loss after obesity surgery (RYGB, VSG, AGB)

a. Eating behaviour

i. Reduction in energy intake

The setpoint theory supports the notion that an individual's body weight trajectory during life is predominantly influenced by their genetic make-up, which interacts with non-biological factors (e.g., social, psychological) to determine the final phenotype [10]. Any weight loss below or above the set-point is perceived as an alarm signal by the areas of the brain that regulate energy intake and expenditure, such as the hypothalamus and brainstem [11]. These areas are located in the subcortical areas of the brain involved in automated function like respiration or body temperature. The hypothalamus and brainstem receive continuous and highly accurate humoral and neural signals from adipose tissue, stomach, intestine and pancreas regarding body energy stores and acute energy intake respectively. Upon weight loss, these messengers change and [12] signal depletion of body energy stores which is disadvantageous from an evolutionary perspective. The final common pathway of this mechanism is the defence of the individual's body weight setpoint through an increase in hunger and reduction in satiety which trigger the executive function areas located in the cortical areas of the brain to seek and consume food.

A good example of how this system is activated is intentional weight loss through caloric restrictive diets. People on severe caloric restriction frequently report a decrease in hunger and increase in satiety during the acute phase of negative energy balance. However, the vast majority find it difficult to maintain the weight they have lost when it plateaus during the stable energy balance phase. This is despite the cortical areas of the brain that control dietary restraint working intensely to maintain the body weight lost. The increase in hunger and decrease in satiety signalled by the hypothalamus/ brainstem results in an increase in caloric intake which eventually leads to the regain of weight lost and in many cases the establishment of a new setpoint which is higher than the original baseline [12].

Repeated cycles of this process increase body weight setpoint, making it progressively harder to achieve sustained weight loss [13]. Consequently, any successful weight loss *and* maintenance therapy should be sophisticated enough, from a biological perspective, to counteract this elaborate body weight regulation system.

Obesity surgery has proven to be biologically very sophisticated and is thus an effective therapy. Similar to caloric restriction during the acute negative balance phase, patients after surgery report a decrease in hunger and increase in satiety [14]. The key difference between dieting and obesity surgery is that after surgery, the body weight setpoint is reduced by approximately 20-30% [15]. Manipulation of the stomach and the small intestine result in favourable changes in humoral and neural signals from the gut to the brain that are conducive to the maintenance of this newly established body weight setpoint.

The comparison of patients' reports and actual weight during the plateau phase of weight loss during dieting vs. obesity surgery is intriguing. Even after surgery, patients report an "alarming" increase in hunger and decrease in satiety during the stable energy balance phase and indeed this translates in both higher energy intake during meals and an increase in meal frequency [16]. Yet, body weight increases only marginally and never reaches the pre-operative value in the majority of cases. Whilst at this new set point, the intensity of the internal feelings of hunger and satiety might return to almost pre-operative levels, altered signalling from the gut acts continuously to reduce total energy intake during a 24-hour period in order to robustly defend the new normal [12].

Patients losing weight through pharmacotherapy (e.g. with glucagon-like peptide 1 (GLP-1) receptor agonists) report very similar changes in their appetite during the acute and chronic phase of their weight loss journey [17]. The only difference is that the effect size of pharmacotherapy is lower than that of surgery, and that is because medications change only one or few of the signalling pathways in the appetite centres of the brain.

Weight loss after the biliopancreatic diversion further highlights that the mechanisms through which these operations work are physiological and not “cognitive" in nature. This procedure is the most effective operation for weight loss, but rarely performed these days due to the associated severe nutritional complications. The very long intestinal bypass in this procedure results in frank macronutrient malabsorption and weight loss. The brain appetite centres rapidly detect this and compensate by *increasing* hunger. Patients after the biliopancreatic diversion commonly consume more calories compared to before their operation. However, even this hyperphagia is not enough to compensate for the severe loss of calories through the gut which is therefore the dominant mechanism causing weight loss.

Neural correlates of reduction in energy intake

The hypothalamus is a critical brain area that controls energy intake and expenditure via two sets of antagonistic neurons: agouti-related peptide (AgRP) neurons to promote hunger and pro-opiomelanocortin (POMC) neurons to promote satiety [18] (Figure 1). Neuropeptide Y (NPY) is secreted by AgRP neurons and is an orexigenic factor. Hypothalamic gene expression of *Agrp*, *Npy* and *Pomc* changes following RYGB surgery [19, 20], but the findings are not consistent and often lack a weight-

matched calorie restricted model. Expression levels of hypothalamic *Agrp* in obese female rats are upregulated when compared to lean controls, but go down to levels similar to lean animals following RYGB. Gene expression of *Pomc* does not change [21]. A recent study investigated the expression of hypothalamic NPY and AgRP in obese mice, following RYGB and compared the results to a weight-matched model. During the first two post-operative weeks, when the peak weight loss was observed, hypothalamic *Agrp* and *Npy* gene expression did not increase compared to mice undergoing sham surgery, suggesting that compensatory hunger signals in the RYGB mice were not activated. In contrast, when the same amount of weight loss was achieved by caloric restriction in a different group of mice, increased expression *of Agrp* and *Npy* was observed. Of note, *Pomc* expression was not altered to a similar degree as *Agrp*, indicating that RYGB suppresses the adaptive hunger response triggered by weight loss [22-24]. Similarly, VSG does not change *Npy* and *Agrp* gene expression in obese rats 4 weeks after surgery [25]. A study that compared VSG and AGB-treated obese rats six weeks after surgery showed that the hypothalamic expression of *Npy* was significantly lower and the expression of *Pomc* was significantly higher in the VSG group [26]. Given the similar post-operative time points, any discrepancies between these studies' findings on *Agrp, Npy* and *Pomc* may be due to rodent strain, differences, diet type and length of exposure, and variations in surgical technique.

The brainstem is the other key player in the obesity surgery-induced suppression of hunger. The strong orexigenic drive stemming from arcuate AgRP/NPY neurons may partly result from inhibition of an equally strong feeding anorexia circuit organized around the lateral parabrachial nucleus (lPBN) and brainstem [27, 28]. Measurement of meal-induced neuronal activation by means of c-Fos in obese mice showed that

brainstem anorexia circuit may have a potential role in adaptive neural and behavioural changes involved in the strong early suppression of energy intake after RYGB [29].

These findings from animal models support the observations from humans in that the direction of change in expression of neuropeptides in the hypothalamus and brainstem after RYGB and VSG is opposite to dieting and favour the maintenance of a lower body weight set point.

Neural signalling

The mechanism of action of AGB is thought to be exclusively through vagal signalling. Injection of fluid through the subcutaneous port increases the extra-luminal pressure on vagal afferents, sending an anorexigenic signal to the brainstem, even in the fasting state [30]. This mechanism is further exaggerated through the increase in fundal intra-luminal pressure exerted by the consumption food, leading to early satiety during a meal. It is common for healthcare professionals to inject progressively more fluid in the AGB in patients not losing enough weight. This eventually leads to mechanical restriction and vomiting. This is a preventable complication that should be avoided, and instead an early decision should be made to remove the AGB in patients who do not respond. More patients do not respond to the AGB compared to RYGB/VSG [31] because the AGB activates only one signalling system to the brain, as opposed to the plethora of anorexigenic signals after RYGB/VSG. A study in rats suggested that signals carried by vagal afferents from the mid and lower small intestine contribute to the early RYGB-induced body weight loss and reduction of food intake [32]. Disruption of vagal afferents and/or efferents

takes place during RYGB and VSG surgery; whether this affects appetite and post-operative weight loss remains unclear. Some studies suggested that vagal sparing surgical technique affects body weight loss in rodents, and therefore the vagal nerve should be preserved during the gastric bypass operation [33, 34]. However, there are limited data on the role of vagus nerve dissection in RYGB and VSG with regards to body weight in humans [35].

ii. Food selection

After RYGB and VSG surgery, but not AGB, some patients also change their food selection [36]. This includes a shift in preference from energy-dense sweet and fatty food to less energy-dense options. The majority of research in this area has used indirect measures of behaviour, e.g. questionnaires, food diaries and verbal report at recall sessions. Whilst these have suggested that the reduction of the consumption of energy dense food might be an additional weight loss mechanism after surgery, they have also demonstrated large variations in response and substantial heterogeneity in findings [37]. This is particularly noticeable in the longer-term measurements of eating behaviour, 5-10 years after surgery when any early changes in macronutrient selection tend to dissipate.

Only a small number of studies have used direct measurements of eating behaviour, i.e., observing the participant's choices during an ad libitum meal or an eating behaviour task. The best evidence so far suggests that patients who lost more weight were those who consumed a lower percentage of fat and low-glycaemic index

foods, and higher percentage of protein as a proportion of their total daily caloric intake [38].

The reduction in the rewarding properties of food is one of the mechanisms that underpins the changes in food selection (Figure 2). This mechanisms has been investigated using functional neuroimaging. Functional Magnetic resonance imaging (MRI) and Positron Emission Tomography (PET) studies provide information both with respect to the direction of change and the areas of the brain reward system that correlate with changes in observed or reported eating behaviour. Notwithstanding discrepancies between studies, there is some agreement that there is a reduction in the activation of brain areas that respond to the involved cues with rewarding properties (e.g. food pictures) after RYGB and VSG [39, 40]. The effect size of this reduction is more pronounced after RYGB compared to VSG [41]. Gut hormones are mediators that underlie this observation, as the blockage partly reverses the reduction in activation of these brain regions [42]. This is in line with animal and human data demonstrating that gut hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) do not just reduce hunger and increase fullness, but reduce the rewarding properties of food through their direct action on their receptors in brain reward areas [43]. It should be noted that functional neuroimaging findings should be interpreted with some caution as they only measure neural *correlates* of eating behaviour, not behaviour itself. The available paradigms also do not allow enough granularity as to whether measured brain responses to food pictures reflect appetitive or consummatory behaviour.

Altered taste function is another mechanism underlying the changes in food selection after RYGB and VSG. With regards to the sensory domain of taste, acuity for sweet

taste is heightened only in the early post-operative period. [44]. It is therefore unlikely to be responsible for long term effects. Selective changes in the appetitive reward value of sweet/fatty taste have also been reported in humans three months after RYGB and VSG, i.e. during the acute phase of negative energy balance [45, 46], but these findings have not been replicated in animal models of RYGB during the stable energy balance phase [47]. The valid measurement of the consummatory reward value of taste is challenging in humans as it relies entirely on the use of indirect measures like visual analogue scales (VAS). Studies using VAS after RYGB surgery have shown discrepant results [44, 48]. There is more consistency in the rodent literature, in which orofacial responses, a good marker of consummatory responses, increase for low concentrations of glucose and decrease for high concentrations of glucose after RYGB [49, 50]. The third domain of taste function is termed digestive preparation and salivation is a marker of this reflex response to tastants. Rates of salivation correlate with the rewarding aspects of the tastant and people with obesity demonstrate higher salivation rates to normal-weight controls [51]. Attempts have been made to measure salivation rates after obesity surgery but with mixed results [52]. Our group's experience with measuring salivation rates in humans is that the available methodologies suffer from low reproducibility (unpublished data).

Neural signalling also contributes to changes in the rewarding value of fat and sugar after surgery. This was investigated in obese rats undergoing RYGB as they were found produce less of the fat-satiety molecule oleoylethanolamide in the small intestine, and this effect was associated with vagus nerve-driven increases in dorsal striatal dopamine release [53]. Inhibition of local oleoylethanolamide, vagal, and dorsal striatal dopamine-1 receptor signalling was inhibited, the beneficial effects of RYGB on fat intake and preferences was reversed.

Post-ingestive neural signalling, in the form of what is widely known as dumping syndrome, may contribute to the underlying reductions in high-glycaemic index or fatty food after RYGB, and less so after VSG. Patients report unpleasant sensations of nausea, sweating and dizziness early after consumption of sugary or fatty foods, which in some people may result in conditioned taste avoidance [54]. During this learning process, these unpleasant symptoms are presumably generated through osmotic shifts between the intestine and circulation, and altered neural signalling. These symptoms are usually associated with the ingestion of specific foods. This does not lead to the complete extinction of these foods from regular consumption, i.e., aversion, but rather their avoidance. Thus the foods remain pleasant to the subject but only when consumed in smaller quantities [54]. It should be noted that dumping syndrome is not present in all patients after RYGB and it may indeed be the case that its impact dissipates over time. This might be due to intestinal adaptation that continues to take place for years after surgery. Dumping is less common after VSG and AGB [55], operations not involving duodenal bypass.

Overall, the available data suggest that changes in food selection take place in a proportion of people after RYGB and VSG, but not after AGB. In the former, this mechanism could compliment the reduction in hunger and increase in satiety to cause additional weight loss. Whether this mechanism persists over time or dissipates following intestinal adaptation remains uncertain. The process of learning to avoid foods that generate unpleasant post-ingestive effects has a greater impact than taste function in shaping food preferences after surgery. Some of the above unresolved questions could be answered using residential stays in facilities that allow human eating behaviour to be as close to normal as possible. Such

experiments could be conducted both early and late after surgery and complimented by studies in animal models of surgery.

b. Energy Expenditure

Enhanced energy expenditure after obesity surgery may be a contributing mechanism to weight loss. Resting energy expenditure has been measured in humans following RYGB, and most recent studies using indirect calorimetry show resting energy expenditure to either decrease within the first post-operative year [56-58], remain stable [59] or even slightly increase [60]. These changes are reported to be highly dependent on organ-tissue body composition as RYGB patients maintain a larger high-metabolic rate organ mass than non-operated controls [59]. Moreover, the acute weight loss following obesity surgery was found to affect the accuracy of energy expenditure predictive equations [61].

A small number of studies used 24-hour indirect calorimetry, a method that is optimal for measuring substrate oxidation because each subject can freely move, consume meals, and engage in physical activity. One study reported that diet-induced energy expenditure in patients 20 months after RYGB was increased, which resulted in an increased contribution to total energy expenditure over 24 hours from an average 12.9 cal/min/kg to 14.7 cal/min/kg, when corrected for total tissue mass, including total adipose tissue, lean body mass, bone mineral density and bone mineral content [62]. Another study reported no changes in 24-hour or diet-induced energy expenditure 11 weeks after RYGB, although this was not corrected for total tissue mass [63]. Nine-years after RYGB, patients had greater diet-induced energy expenditure and total

24hour energy expenditure at an average of 16.9 cal/min/kg when compared to Vertical Banded Gastroplasty patients, a procedure similar to AGB, at 14.9 cal/min/kg [64]. At a shorter follow up period, 24-hour energy expenditure was significantly decreased from baseline to eight weeks post-treatment in patients who underwent RYGB, VSG, AGB and very low-calorie diet, following adjustment for decreases in fat-free mass and fat mass. However, this effect persisted up to one year only after RYGB and VSG (RYGB, −124 ± 42; VSG, −155 ± 118 kcal/d) [65]. Additionally, patients who underwent biliopancreatic diversion (consisting of a horizontal gastrectomy with a distal Roux-en-Y reconstruction resulting in an alimentary limb of 250 cm and a common channel of 50-100 cm) demonstrated increased diet-induced (11.0% at baseline to 19.9% of caloric intake) and physical activity (8344.3 at baseline to 9701.4 kcal/24hr) related-thermogenesis at 6-months postoperatively, when compared to an unoperated control group [66]. One mechanism which may contribute to increased energy expenditure during a meal in humans may be the enhanced glucose utilisation by the hypertrophied small intestine [67]. However, absolute energy expenditure is reduced after surgery in humans and the increase in energy expenditure expressed per total body mass may be at least in part explained by change in body composition (i.e. increased lean to fat mass ratio).

The type of diet may also affect measurements of energy expenditure. A randomised clinical trial in patients following diet-induced weight loss showed that lowering dietary carbohydrate intake increases energy expenditure during weight loss maintenance [68]. However, meta-analysis of 32 controlled feeding studies with isocaloric substitution of carbohydrate for fat found that both energy expenditure and fat loss are greater with lower dietary fat [69].

Contrary to observations in humans, the majority of studies in rodent models of RYGB report an increase in total energy expenditure when compared with *ad libitum*-fed shams and weight-matched shams. This has been measured at different post-operative time points using indirect calorimetry or validated mathematical formulae [70-73]. VSG appears to induce no change in total energy expenditure [25, 71, 73]. However, indirect calorimetry produces an absolute error as high as 38% when compared with standard direct calorimetry [74]. A recent study [75] used a combination of sensitive direct and indirect calorimetry to overcome this limitation and demonstrated an increase in resting energy expenditure after RYGB, but not VSG.

Brown adipose tissue (BAT) is a major player in regulating energy metabolism by thermogenesis and triglyceride clearance [76, 77] and plays a role in energy expenditure changes after obesity surgery. A decrease in triglyceride content, coupled with increased proportion of brown adipose tissue in the supraclavicular fat depot was found in women six months after RYGB and VSG [78]. However, the role of BAT in energy expenditure following obesity surgery has mainly been studied in rodents. The expression of key BAT thermoregulatory genes such as uncoupling protein-1 (UCP-1), remain unchanged following RYGB but are reduced in caloric-restricted weight-matched animals [79], and that the bypassed duodenum has a key role in the observed postoperative metabolic profile [80]. The volume and metabolic activity of BAT, as recorded by micro-positron emission tomography/computed tomography increased following RYGB, but not after AGB and VSG [81]. A proposed mechanism for the metabolic activity of BAT is an observed increase in growth hormone/insulin-like growth factor-1, which regulates adipocyte differentiation [81]. Unlike VSG, RYGB causes an increase in total resting metabolic rate, as well as a specific increase in splanchnic sympathetic nerve activity and “browning” of visceral mesenteric fat via

endocannabinoid signalling within the small intestine [75]. Although *in vivo* studies are vital to unravel the mechanisms of energy expenditure difference after obesity surgery, it is important to note the species difference between mice and rats, as well as strain differences in a single species. There are also differences between rodent and human BAT, in terms of depot locations, beige and brown adipose tissue amount and thermogenic capacity [82]. Despite this, UCP1 content and function are similar between human and mouse BAT [83].

Overall, it remains unclear from the existing evidence to what extent, if at all, post-operative weight loss is driven by enhanced energy expenditure after RYGB and VSG versus dietary calorie restriction, as energy metabolism is closely associated with body weight changes. The discrepancy on energy expenditure values reported in the discussed studies could indeed be due to differences in diet, patient body composition and energy expenditure measurement. These uncertainties suggest to us that the physiological contribution of energy expenditure to weight loss after RYGB and VSG is small in comparison to the dominant contribution of reduced energy intake.

Mediators underlying changes in energy intake and expenditure after obesity surgery

a. Gut hormones

Gut hormones are secreted in response to nutrient ingestion and regulate energy balance and glucose homeostasis by signalling to the pancreas but also by direct

and indirect action in the brainstem and the hypothalamic arcuate nuclei [84]. Two anorexigenic gut hormones that have been widely investigated after obesity surgery are GLP-1 and peptide YY (PYY) which are secreted by the enteroendocrine L-cells across the gastrointestinal tract [14].

Both GLP-1 and PYY are elevated post-prandially after RYGB and VSG, and the enhanced secretion has been hypothesised to be a key mediator of the observed post-operative increase in satiety [85]. Fasting concentrations do not change significantly, suggesting that they are not the mechanisms underlying the reduction in hunger. The absence of mechanical restriction at the level of the gastro-jejunal anastomosis after RYGB enables the rapid delivery of nutrients to the jejunum and ileum, where the highest number of enteroendocrine (primarily GLP-1 secreting) L-cells are located, triggering the enhanced secretion of anorexigenic gut hormones [86]. These exert their action in the brainstem/hypothalamic system through stimulation of intestinal vagal afferents and by crossing the blood-brain barrier. Despite the absence of intestinal bypass, VSG is thought to engage the same mechanism through the rapid emptying of the high-pressure gastric remnant [87], thus creating a functional intestinal bypass. However, the post-prandial increase in anorexigenic gut hormones after VSG is lower to that observed after RYGB [88]. This might explain differences in the weight loss efficacy of the two interventions and substantial weight regain after VSG at long term follow-up. Despite the persistent rapid delivery of nutrients to the distal small intestine, there is no compensatory decrease in the L-cell numbers after RYGB [86]. In contrast, following intestinal adaptation L-cell numbers increase, further amplifying anorexigenic signalling. The density of enteroendocrine cells in the distal small intestine does not change as the intestinal volume also increases through hypertrophy [86].

Combined blockade of both GLP-1 and PYY via single infusion of antagonists increases energy intake, pointing at their appetite-suppressing role in humans after RYGB [89]. These findings are in line with experiments in which the administration of the somatostatin analogue octreotide following RYGB and ABG in humans resulted in suppression of postprandial secretion of PYY and GLP-1 and reduction in energy intake only in the RYGB group [14].

Chronic infusion of the selective GLP-1 receptor antagonist exendin-(9-30) into the lateral cerebral ventricle significantly increased energy intake and body weight in both RYGB and sham-operated rats, while chronic infusion of a selective Y2-receptor antagonist had no effect in either group [90]. However, obese GLP-1R-deficient mice (GLP-$1^{-/-}$) lost the same amount of body weight and fat mass and maintained a similarly lower body weight compared with wild-type mice, following RYGB [90]. This observation indicates low importance of GLP-1R in appetite regulation and this was further confirmed by blocking peripheral and central GLP-1R action in RYGB and sham obese mice using exendin-(9-30), which did not reverse the weight loss effect of RYGB or influence the weekly body weight gain in sham mice [91]. Similarly, obese Y2-receptor deficient mice ($PYY^{-/-}$) also responded similarly to RYGB compared to wild type mice for up to 20 weeks after surgery, with initial hypophagia and sustained body weight loss. Weight-matched Y2-R knockout mice showed the same improvements to RYGB as seen in wild type mice, suggesting that PYY signalling through Y2 receptor alone is not responsible for the appetite-suppressing and body weight-lowering effects of RYGB [92]. However, acute administration of exendin-(9-30) with a selective Y2-R antagonist increased high fat food preference additively in RYGB-operated but not in sham-operated diet-induced obese rats [93]. This is in agreement with human studies [89, 94] and indicates a

differential effect of antagonists when administered alone versus in combination, as well as acutely versus infused chronically. This also contrasts an acquired effect associated with antagonist infusion , compared to the genetic state associated with deficiency of the Y2 receptor or GLP-1 receptor in knockout models.

Recent studies have focused on two additional gut hormones: oxyntomodulin and glicentin, products of the pre-proglucagon gene also released from enteroendocrine in response to food transit. Oxyntomodulin is a dual agonist of glucagon and GLP-1 receptors that may act additively to GLP-1 to reduce food intake and appetite[95]. Glicentin protein sequence contains the sequence of oxyntomodulin and lthough its biological role is not yet clear, it is hypothesized to be the most stable of the proglucagon peptides and therefore may serve as the best marker of the secretion of L-cell hormones, such as GLP-1 [88]. Postprandial levels of oxyntomodulin and glicentin were significantly increased three months after VSG or RYGB, but not after AGB, in humans, and these elevated concentrations were positively associated with feeling of satiety and weight loss [96]. These results were later replicated by Nielsen et al, who reported that elevated circulating levels of oxyntomodulin and glicentin predicted weight loss and were positively associated with a decreased preference for energy-dense foods [88].

Changes to plasma concentration of the orexigenic hormone ghrelin after RYGB remains controversial. Studies in humans have demonstrated that hormone levels are increased, decreased or stay the same [97]. The results of studies measuring ghrelin after VSG are more consistently demonstrating a decrease in the post-prandial concentrations of the hormone [97]. Thus, the contribution of ghrelin reductions in weight loss might be more relevant after VSG than RYGB.

b. Bile Acids

Bile acids have long been known to play an important role in dietary lipid absorption and cholesterol catabolism and have been shown to increase energy expenditure by promoting intracellular thyroid hormone activation [98]. Bile acid function is mediated by two primary gut receptors, Takeda G-protein receptor 5 (TGR5) and farnesoid X receptor A (FXR). These receptors stimulate the postprandial release of fibroblast growth factors 19 and 21 (FGF19/21) [99]. FGF19 is released from the small intestine post-prandially and decreases bile acid secretion, while FGF21 is secreted by the liver during fasting and has a role in energy homeostasis maintenance, as well as controls glucose and lipid metabolism (Figure 3). Circulating FGF19 levels have been shown to be lower in people with obesity compared to healthy control subjects [100], while administration of human FGF19 in obese mice induced a significant dose-dependent decrease in body mass which was associated with a decrease in the concentrations of triglycerides, as well as increased fatty acid oxidation and brown tissue mass [101]. Following the release of FGF19, the role of subsequent neuronal FGF receptor activation has also been linked to body weight regulation, as it signals an energy-replete state to hypothalamic AgRP/NPY neurons [102]. In contrast, FGF21 is elevated in people with obesity [103], and obese mice are insensitive to exogenous FGF21 administration, suggesting that obesity is an FGF21-resistant state [104]. However, FGF21 sensitivity is restored in humans following weight loss [105]. Although not directly correlated with obesity, FGF21 variants are associated with increased sweet consumption, as plasma FGF21 levels increase acutely after oral sucrose ingestion. This indicates that FGF21 could influence eating behaviour [106].

Total bile acids and FGF19 increase after RYGB and VSG in humans and rodents [107]. Specifically, glycine-conjugated serum bile acids increased acutely following RYGB in humans, while both conjugated and unconjugated bile acids increased after VSG, an effect not replicated in an unoperated calorie-restriction control group [108, 109]. The bile acid increase is sustained five years after surgery, with higher levels associated with greater weight loss, and lower total cholesterol [110]. Apart from their role in energy expenditure increase [98] and fatty acid oxidation [101], bile acids are thought to have an appetite-inhibitory effect, as they stimulate the secretion of GLP-1 and PYY [111]. However, serum bile acids, FGF19 and GLP-1 concentration all decreased in patients who achieved lifestyle-induced weight loss, further pointing to the fact that dieting and obesity surgery-induced changes in body weight are triggered by different mechanisms [112]. Discrepancies exist regarding the post-operative timing of bile acid increase, as some studies report an acute effect [109] whether others observe a gradual increase 1 year following surgery [113, 114]. Concentrations of FGF21 after surgery remain more controversial between different studies, possibly because circulating concentration and sensitivity changes are shown to be secondary to weight loss which can differ widely [99, 115-117].

A growing body of evidence suggests that circulating bile acids act as signalling molecules that control both their own synthesis and multiple metabolic pathways by targeting the transcription factor FXR and the membrane protein TGR5. FXR appears to be key in post-operative weight loss, as it controls the transcription of genes involved in fatty acid and triglyceride synthesis and lipoprotein metabolism [118] and promote adipose tissue browning [119]. *In vivo* studies involving genetic disruption of FXR in mice that then underwent VSG demonstrated that the receptor is a molecular target for beneficial effects of surgery as it contributes to the maintenance

of weight loss following VSG. Specifically, FXR-knockout VSG mice consumed more energy than sham operated controls suggesting that FXR signalling is necessary for the repression of rebound hyperphagia following caloric restriction initially achieved by VSG [120]. Studies in mice also investigated the role of TGR5 receptor in post-operative weight loss, as its activation can increase postprandial GLP-1 secretion in the lower intestine [121, 122]. Similar to FXR studies, TGR5 knockout mice demonstrated reduced weight loss following VSG. Moreover, body composition analysis revealed no differences between wild type TGR5-knockout sham and VSG mice at 14 weeks after surgery, indicating that TGR5 is required to maintain weight loss and fat mass reduction after VSG [123]. A possible mechanism of this is a TGR5-driven mitochondrial separation and turnover of white adipose tissue to beige, as administration of TGR5-selective bile acid mimetics to thermoneutral housed mice led to the appearance of beige adipocyte markers and an increase in mitochondrial content [124]. However, not all studies report a reduction of weight loss following VSG and RYGB in TGR5 knockout mice [125, 126]. A possible explanation for this is the rate of weight regain following obesity surgery, and as a result, the type and length of exposure to high-fat diet in pre-operative mice. Most studies investigating the role of the TGR5 and FXR receptors were conducted in animal models, and their roles may be different in humans.

Overall, the role of bile acids on post-operative weight loss is not yet fully understood. As the extent to which energy expenditure drives weight reduction following obesity surgery remains unclear, the ability of bile acids to increase GLP-1 secretion [111] and the role of FGF19 on hypothalamic AgRP/NPY neurons [102] indicate an indirect anorectic effect as the main course of action after RYGB and VSG.

c. Gut microbiota

Gut microbiota have a vital role in both energy harvesting and energy expenditure. They can metabolize indigestible complex carbohydrates by fermentation, leading to the production of short-chain fatty acids, as well as control the absorption of nutrients [127, 128]. Gut microbiota also play a role in the thermogenic capacity of brown adipose tissue and the turnover of beige adipocytes, as mice lacking gut microbiota have been reported to have impaired UCP1-dependent thermogenesis in cold, and oral gavage of the bacterial metabolite butyrate was able to rescue the effect with BAT recruitment [129].

Obesity is often characterised by gut dysbiosis, as defined by substantial modifications in the gut microbiota composition and low microbial gene richness [130]. Firmicutes and Bacteroidetes are the two dominant gut microphyla associated with obesity [131], and the Firmicutes/Bacteroidetes ratio correlates with increased body weight [132]. Together these phyla account for 90% of the microbiome, with the remaining groups separated mainly into Actinobacteria, Proteobacteria and Verrucomicrobia [133]. *Akkermansia muciniphila* of class Verrucomicrobia has also been correlated with obesity in humans [134].

The mechanism via which obesity surgery achieves weight loss may include changes in gut microbiota. Transfer of gut microbiota from RYGB-treated mice to non-operated, germ-free mice resulted in weight loss and decreased fat mass in the recipient animals when compared to recipients of microbiota induced by sham surgery [135]. In rats transplanted with the RYGB-microbiota, this decrease in adiposity

and body weight was not associated with a change in food intake, further suggesting that the RYGB-associated gut microbiota either increase energy expenditure or have reduced ability to harvest energy from nutrients [135]. Stool transplantation from patients after RYGB or Vertical Banded Gastroplasty (VBG) to germ-free mice promoted reduced fat deposition and weight gain when compared to a control group that was colonized with stools from patients with obesity [136]. Mice colonised with obesity surgery microbiota also had a lower respiratory quotient, indicating decreased utilization of carbohydrates as fuel [136].

Although human studies [137, 138] have reported differences in gut microbiota post-operatively, the extent of these changes varies. This could be due to patient inclusion criteria, such as glycemia state and medication, but also diet, and type of procedure. However, studies in humans consistently demonstrate an increase in gut microbiota diversity, spatial organization and stability, and specifically Proteobacteria, after RYGB (Table 1). Gut microbiota diversity is a measure of how many different species exist and how evenly distributed they are in the gut community, and low diversity is a sign of dysbiosis [139]. Some studies also reported a decrease in Firmicutes and Bacteroidetes phyla in humans and rats post RYGB [136, 140, 141]. Increase in gut microbiota diversity, stability and resilience is important, as a large number of associations between gut microbiota and adipose tissue gene regulation as early as three months after surgery [136, 140, 142] have been reported, further demonstrating that gut microbiota may play a direct role in the control of adiposity by regulating lipid metabolism. Moreover, gut microbiota lead to the production of short-chain fatty acids, which stimulate GLP-1 secretion via free fatty acid receptor-2 (FFAR2), and therefore may also reduce energy intake [143].

A decrease in Proteobacteria was recorded in patients following VSG [144] and AGB [145]. This differential effect between VSG and RYGB could be a result of duodenal exclusion in RYGB, as duodenal-jejunal bypass with minimal gastric resection in obese rats increased microbial richness and abundancy when compared to rats treated with GLP-1R agonists [146, 147]. This has also been observed in humans following treatment with the endoscopic duodenal-jejunal bypass liner [148] [149]. Comparison of AGB, pharmacologically induced weight loss and RYGB demonstrated that at similar weight loss, the greatest alteration in gut microbiota diversity occurred after RYGB [145, 150].

Despite the positive effect on weight loss through a combination of mechanisms discussed above, RYGB is unable to fully reverse the decreased gut microbial gene richness and compositional changes observed in patients with obesity [151]. Interventions such as faecal transplantation from lean donors to patients with obesity revealed that weight-lowering beneficial effects are linked to changes in plasma metabolites and driven by baseline faecal microbiota composition [152]. Moreover, gut microbiota diversity alteration accelerates post-dieting weight regain [153], suggesting that microbiome-targeting approaches may help enhance weight loss after surgery or prevent weight regain.

Genetics and Obesity Surgery

Patient selection for surgery (“personalized medicine”) may provide an additional refinement for existing procedures and could lead to the identification of genes or pathways which might provide useful therapeutic targets. Candidate gene studies have explored roles for the melacocortin-4 receptor (MC4R) [154], revealing greater

638 weight loss in patients whose obesity is in part driven by mutations in this gene. A
639 more recent genome-wide association study (GWAS) [155] has reported 17 single
640 nucleotide polymorphisms (SNPs) in weight loss two years post RYGB, implicating
641 roles for the 5-hydroxytriptamine receptor 1A and other genes. Whether the strength
642 and number of these associations is substantial enough to provide predictive power
643 is unclear.

644

645 **Conclusion**

646

647 The anatomical manipulations during the most frequently used obesity surgery
648 procedures cause weight loss through changes in the biology of the gut. Altered
649 signalling from the gut to the brain, the organ responsible for the disease of obesity,
650 facilitate reductions in energy intake and in some people changes in food selection.
651 Increased or unaltered energy expenditure in the context of weight loss may also
652 contribute to the defence of a new body weight set point. The precise mechanisms
653 underlying these profound changes are not completely understood. Unravelling of
654 the elusive physiology of the gut after surgery will help optimise surgical procedures,
655 develop non-surgical therapies, address weight regain after surgery, but also
656 understand the pathophysiology of the disease of obesity itself.

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Table 1: Summary of selected publications reporting gut microbiota changes following bariatric surgery.

Graphical Abstract: Representation of the main physiological mechanisms underlying weight loss following Vertical Sleeve Gastrectomy (VSG) and Roux-n-Y Gastric Bypass (RYGB). Abbreviations: GLP-1, glucagon like peptide-1; PYY, peptide YY. Figure was created using Servier Medical Art.

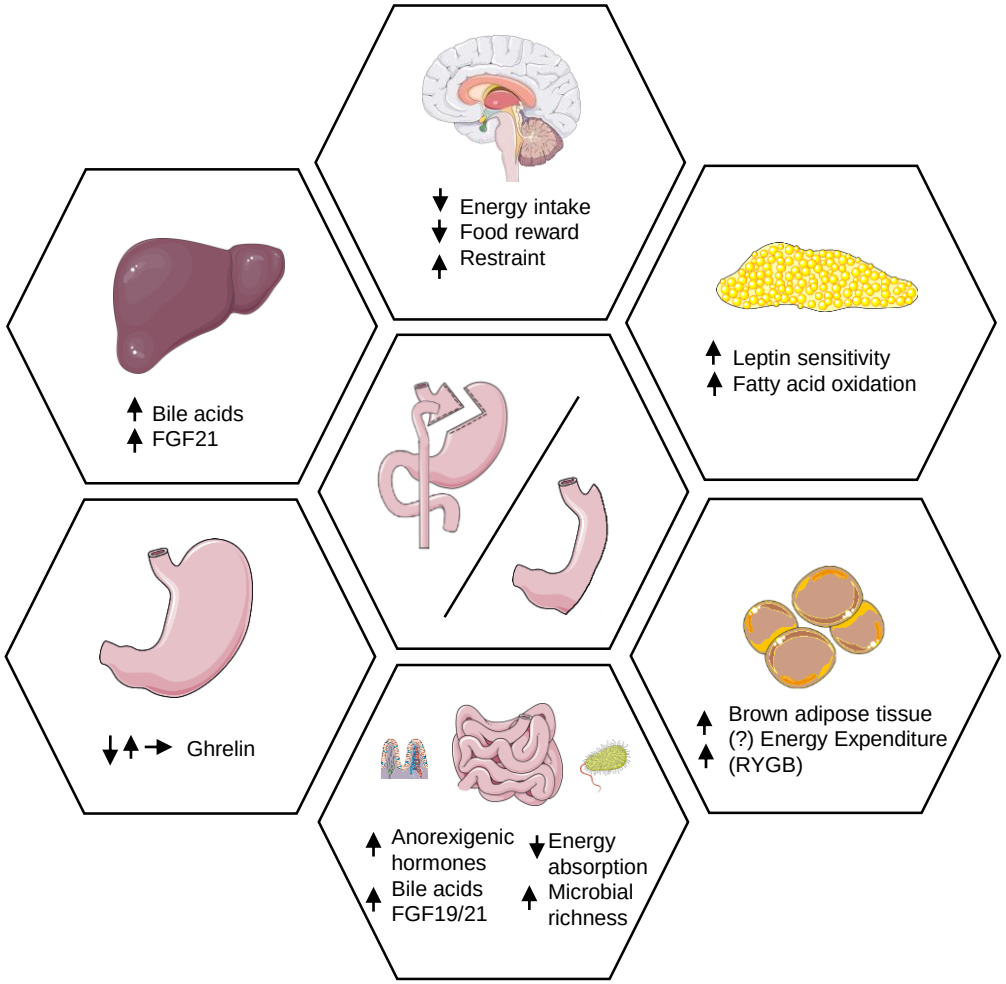
Figure 1: The “AgRP-POMC” model of gut-brain cross-talk. Abbreviations: AgRP, agouti-related peptide; , POMC, pro-opiomelanocortin; NPY, Neuropeptide Y. Figure was created using Servier Medical Art.

Figure 2: Changes in eating behaviour following obesity surgery

Figure 3: Bile acid synthesis and receptor activation following obesity surgery. Abbreviations: FXR, Farnesoid X receptor; TGR5, G protein-coupled bile acid receptor 5; GLP-1, Glucagon-Like Peptide 1; FGF19, Fibroblast growth factor 19. Figure was created using Servier Medical Art.

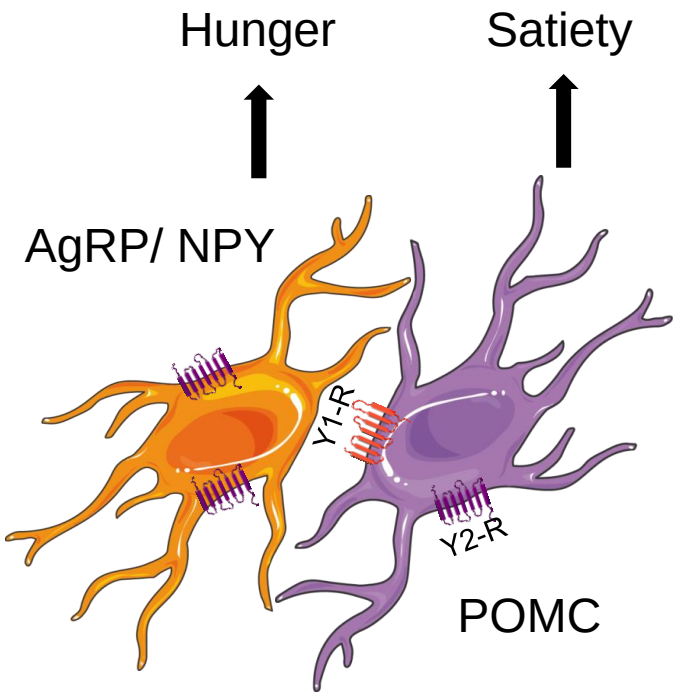
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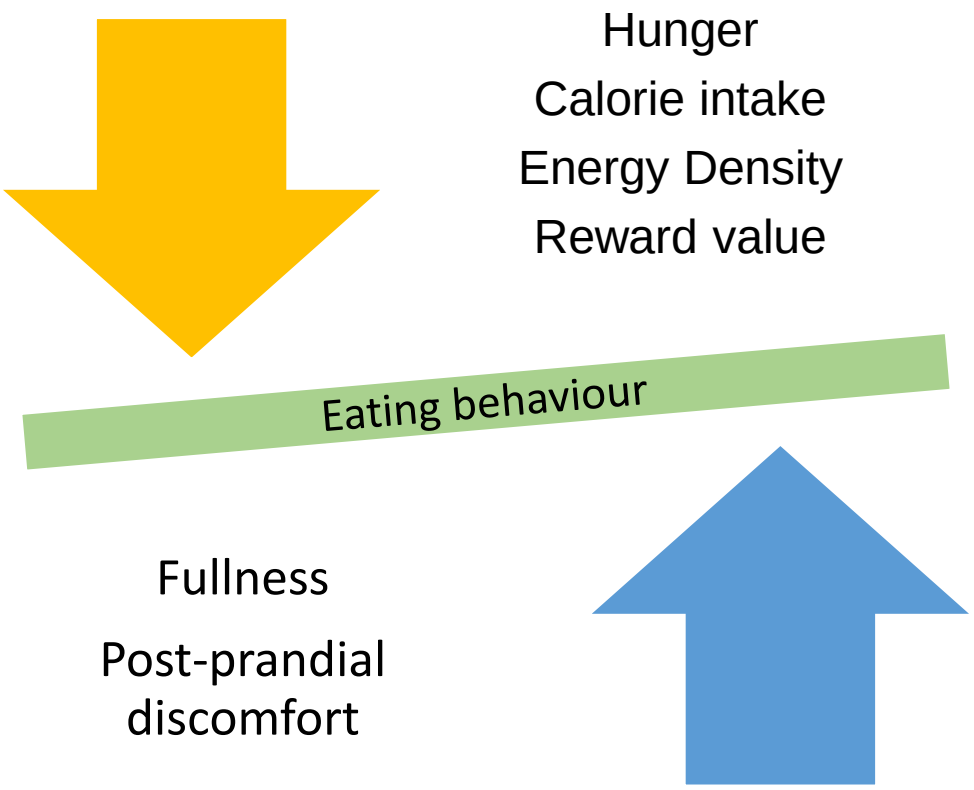
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Figure 1:



Click here to access/download;Figure;Akalestou_figure2.pptx

Figure 2:



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Figure 3:

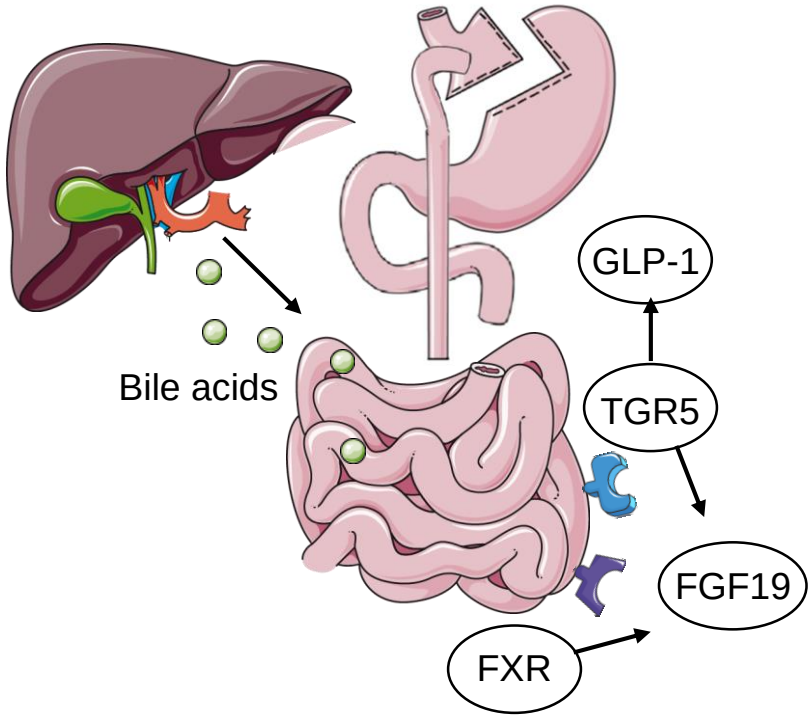


Table1 Click here to access/download;Table;Akalestou_Table1.docx

Table 1:

Author	Species	Procedure	Increased phyla	Comparison	Timepoint
Liou et al, 2014 [135]	mouse	RYGB	Proteobacteria Verrucomicrobia	Obesity, pair fed	0-12 weeks
Tremaroli et al, 2015 [136]	human	RYGB, VBG	Proteobacteria	Obesity	9 years
Graessler et al, 2013 [137]	human	RYGB	Proteobacteria	Obesity	0,3 months
Palmisano et al, 2020 [138]	human	RYGB	Proteobacteria Fusobacteria	Normal weight	0,3, 6 months
Zhang et al, 2009 [140]	human	RYGB	Proteobacteria Verrucomicrobia	Obesity, normal weight	8, 15 months
Li et al, 2011 [141]	Rat (lean)	RYGB	Proteobacteria	Normal weight	2 - weeks
Kong et al, 2013 [142]	human	RYGB	Proteobacteria	Obesity	0, 3, 6 months
Lee et al, 2019 [145]	human	RYGB, LAGB	Proteobacteria Actinobacteria	Medically induced weight loss	9 months
Furet et al, 2010 [150]	human	RYGB	Bacteroides	Obesity, normal weight	0, 3, 6 months

Mechanisms of weight loss after obesity surgery

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Essential points:

- Obesity surgery induces significant weight loss, yet the exact mechanisms remain unclear
- Changes in food selection take place after obesity surgery and this mechanism could compliment reduction in hunger and increase in satiety
- Enhanced energy expenditure may be a contributing mechanism to weight loss, however reports are controversial
- Post-prandial elevated secretion of anorectic gut peptides is considered to be a key mediator of the observed post-operative increase in satiety
- Obesity surgery induces an increase in gut microbiota richness, which may play a direct role in the control of adiposity by regulating lipid metabolism