

Review

Appetite and body weight regulation after bariatric surgery

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Summary

Bariatric surgery continues to be remarkably efficient in treating obesity and type 2 diabetes mellitus and a debate has started whether it should remain the last resort only or also be used for the prevention of metabolic diseases. Intense research efforts in humans and rodent models are underway to identify the critical mechanisms underlying the beneficial effects with a view towards non-surgical treatment options. This non-systematic review summarizes and interprets some of this literature, with an emphasis on changes in the controls of appetite. Contrary to earlier views, surgery-induced reduction of energy intake and subsequent weight loss appear to be the main drivers for rapid improvements of glycaemic control. The mechanisms responsible for suppression of appetite, particularly in the face of the large weight loss, are not well understood. Although a number of changes in food choice, taste functions, hedonic evaluation, motivation and self-control have been documented in both humans and rodents after surgery, their importance and relative contribution to diminished appetite has not yet been demonstrated. Furthermore, none of the major candidate mechanisms postulated in mediating surgery-induced changes from the gut and other organs to the brain, such as gut hormones and sensory neuronal pathways, have been confirmed yet. Future research efforts should focus on interventional rather than descriptive approaches in both humans and rodent models.

Keywords: Aversive conditioning, executive control, food choice, food reward.

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Introduction

It is now generally acknowledged that bariatric surgery is the most effective intervention for the treatment of common obesity and its associated comorbidities. Weight loss is larger and more sustained compared with intensive medical treatment, including drugs and lifestyle changes. Although it is still too early to tell, bariatric surgeries also seem to achieve these beneficial effects without serious side effects and high mortality. To the contrary, the longest running study, the Swedish Obese Subjects Study found

decreased mortality and decreased risk for certain cancers in bariatric surgery patients. The fact that about half of the 16,000 total articles on bariatric surgery (PubMed) were published in just the last 5 years clearly illustrates the rush to identify the biological mechanisms underlying this remarkably efficient obesity treatment. However, despite these intense research efforts in humans and rodent models, we are far from understanding the underlying mechanisms. Early hypotheses such as changes in gut hormone secretion have not yet been confirmed and new candidate mechanisms are being added to the list. This non-systematic

review highlights potential mechanisms contributing to the sustained change in energy balance regulation that allows bariatric surgery patients and rodents to remain at greatly reduced body weight levels.

The role of increased energy expenditure

It is important to distinguish at least two phases of body weight regulation after bariatric surgery, an initial phase of rapid weight loss and a subsequent phase of weight stability or weight regain. Few clinical and rodent studies have measured energy expenditure (EE) during the rapid weight loss phase. The weight loss nadir after Roux-en-Y gastric bypass (RYGB) is typically reached by 6–12 months in humans and 2–3 weeks in rodents. In most of the few human studies with EE measurements at 1–3 months after surgery, before reaching the weight loss nadir, resting

energy expenditure (REE) was consistently decreased by 14–24% compared with before surgery (1–3) (Table 1). Only one study reported that REE was not significantly decreased (~2%) at 6 weeks after RYGB (4). Unfortunately, there are no RYGB rodent studies which have measured REE during the 2–3 weeks of rapid weight loss. Thus, the limited clinical data available suggest that during the rapid weight loss phase, reduced EE is more or less commensurate with weight loss. Because weight loss induced by calorie restriction leads to an adaptive fall in EE (5), it is, however, possible that this fall is blunted by gastric bypass surgery.

Many more studies measured EE during the phase of relative weight stability that follows the rapid weight loss phase after RYGB and other bariatric surgeries (Table 1). In a recent comprehensive review of this literature, Thivel *et al.* concluded that, at least in humans, total EE and REE are decreased after surgery compared with pre-surgical

Table 1 Differences in measurements of energy expenditure and intake at different time points after bariatric surgeries between human and rodent models

		Human	Rodent
Energy expenditure	Weight loss phase (1–6 months in humans and 1–3 weeks in rodents)	<p>↓ ~16, 21 and 21% in BMR at 1, 3 and 6 months, respectively after RYGB (1)</p> <p>↓ ~24% in SMR at 3 months after VBG (2)</p> <p>↓ ~13 and 16% in REE at 3 and 6 months, respectively after RYGB (3)</p> <p>↓ ~2, 8 and 7% in REE at 1.5, 3 and 6 months, respectively after RYGB (4)</p>	NA
	Weight maintenance/regain phase (after 6 months in humans and 3 weeks in rodents)	<p>↓ ~20% at 12 months after RYGB (1)</p> <p>↓ ~28% in SMR at 12 months after VBG (2)</p> <p>↓ ~19% at 12 months after RYGB (3)</p> <p>↓ ~8, 9 and 7% in REE at 1, 1.5 and 2 years, respectively, after RYGB (4)</p> <p>↓ ~25% in REE at 14 ± 2 months after RYGB (7)</p>	<p>↑ ~5% in TEE at 6 weeks after RYGB in rats versus sham-operated <i>ad libitum</i> fed</p> <p>↑ ~13% in TEE at 11 weeks versus sham-operated weight-matched (8)</p> <p>↑ ~18 and 30% in REE at 12–15 weeks after RYGB in rats versus sham-operated <i>ad libitum</i> fed and versus sham-operated weight-matched, respectively (9)</p> <p>↑ ~26% in TEE at 8 weeks after RYGB in mice (10)</p> <p>↑ ~22% in REE at 8 weeks after RYGB in mice (11)</p>
Energy intake	Weight loss phase	<p>↓ ~74, 70 and 63% at 1.5, 3 and 6 months, respectively, after RYGB (4)</p> <p>↓ ~58% at 6 weeks after RYGB (28)</p> <p>↓ ~66 and 63% at 6 months after RYGB and VBG, respectively (29)</p> <p>↓ ~46% at 6 months after RYGB (30)</p> <p>↓ ~80 and 67% at 2 and 8 weeks (29)</p>	<p>↓ until ~4 weeks after VSG (34)</p> <p>↔ at 3 weeks after RYGB in rats (37)</p> <p>↑ ~9% between day 6 and 13 after RYGB in mice (39)</p>
	Weight maintenance/regain phase	<p>↓ ~58, 52 and 47% at 1, 1.5 and 2 years, respectively, after RYGB (4)</p> <p>↓ ~29 and 21% at 2 and 10 years, respectively, after RYGB, VSG and GB (27)</p> <p>↓ ~43 and 34% at 1 and 2 year, respectively, after RYGB (28)</p> <p>↓ ~57, 52, 49 and 47% at 1, 1.5, 2 and 3 years after RYGB (29)</p> <p>↓ ~33% at 1 year after RYGB (30)</p>	<p>↓ ~17% over 5 months after RYGB in rats (9)</p> <p>↔ after 4 weeks after VSG in rats (34)</p> <p>↔ at 4 weeks after RYGB in mice (36)</p> <p>↔ at 14 weeks after RYGB in rats (37)</p> <p>↓ ~7% over 60 d after RYGB in mice (39)</p>

BMR, basal metabolic rate; GB, gastric banding; NA, not applicable; REE, resting energy expenditure; RYGB, Roux-en-Y gastric bypass; SMR, sleeping metabolic rate; TEE, total energy expenditure; VBG, vertical banded gastroplasty; VSG, vertical sleeve gastrectomy.

levels, commensurate with the decrease in both fat mass and fat-free mass (6). Furthermore, these authors concluded that: 'it is not the nature of the bariatric surgery but rather factors such as energy balance status (weight loss, stability, or regain) or body composition that impact the post-operative change in REE' (p. 257). One of the most comprehensive and longitudinal studies measuring EE before and at several time points after RYGB surgery also concluded that 'REE changes were predicted by loss of body tissue; thus, there was no significant long-term change in energy efficiency that would independently promote weight regain' (7).

This conclusion is in stark contrast to at least some rodent studies that claimed significantly increased EE after RYGB but not sleeve gastrectomy in rats (8,9) and mice (10,11). However, much of the difference may be explained by how EE is expressed and to which reference it is compared. Most human studies express EE uncorrected for body weight, while most rodent studies express it per either total body weight or a fractional power function of body weight such as $\text{kcal kg}^{0.75}$. For example, if EE is 10% lower per animal after RYGB and they weigh 25% less compared with sham surgery, correcting for body weight would result in 17% higher EE, and even if using the 0.75 power for body weight, would result in 8% higher EE. While most human studies compare EE after surgery with pre-surgical levels, post-surgical EE in rodent models is always compared with sham-operated or weight-matched animals, not to pre-surgical levels.

In some rodent studies, evidence for increased EE after RYGB is more convincing. First, pair-feeding sham-operated rats with the same amount of food eaten by surgical rats resulted in higher body weight of sham-operated animals. In fact, sham-operated rats had to eat less than surgical rats to maintain the same weight, implicating either increased EE and/or fecal energy loss after RYGB. Direct measurements revealed increased EE and only negligible malabsorption (8,9). Second, a more systematic assessment of energy balance by measuring energy intake, fecal energy loss and the metabolic costs of fat and lean tissue in mice demonstrated higher EE in mice after RYGB (11). Together, these findings suggest that there might be important species differences in EE regulation after bariatric surgery. One caveat to consider is that pair-feeding or weight-matching experiments disrupt natural feeding patterns and that restricted animals typically eat their daily food ration within a short period of time often during the light cycle. This 'unnatural' feeding pattern could have profound influences on energy fluxes and the thermic effect of food that is different from eating smaller amounts of food but throughout the day (12).

The most unbiased way of analysing EE data is multiple linear regression, relating EE to age, fat-free mass and fat mass, three variables most strongly related to EE (13,14).

However, most EE data are collected by indirect calorimetry which calculates EE values using an equation established in healthy animals and based on the assumption that substrate interconversion is negligible (13). There is no guarantee that this equation would work the same way for both morbidly obese, often diabetic patients and patients that have undergone bariatric surgery.

In summary, there is very limited evidence for increased EE as an important factor in weight loss and maintenance after bariatric surgeries in humans. There may be an important species difference with rodents, particularly mice, possibly using increased EE as a strategy to maintain lower body weight after surgery. It will be important in future studies to report EE data always together with detailed body composition data and to run pair-fed and/or weight-matched control groups with normal diurnal intake patterns because only such carefully controlled studies are able to isolate the net effects of surgery.

Mechanisms of increased energy expenditure

Several potential mechanisms for increasing EE after bariatric surgeries have been suggested, but there is no study that directly tested the role of any of them. Bile acids and fibroblast growth factors have been shown to stimulate EE in mice by acting on brown adipose tissue thermogenesis (15) and circulating levels of bile acids and Fibroblast growth factors (FGF) 19 and 21 are increased in both humans (16–18) and rodents (19) after RYGB or sleeve gastrectomy. However, in humans, there are contradictory reports regarding the association of bile acid levels and energy metabolism (20,21).

Intestinal hypertrophy after RYGB (8,22–25) and the resulting increased glucose utilization (26) have also been suggested as a possible mechanism for increased EE.

The role of reduced energy intake

Weight loss phase

There is no doubt that decreased energy intake is the main driver for the initial weight loss phase after all types of bariatric surgeries and in both humans and rodents, even though energy intake studies in humans are complicated by pre- and post-surgical behavioural counselling and by limits in caloric intake and macronutrient composition during the immediate post-surgical period. Thus, clean separation of behavioural modification from biological needs is difficult. Bariatric surgery patients receive a liquid low-calorie diet for the first post-operative week and are instructed to eat low-fat food with low-energy density. Also, food intake is usually measured by non-validated self-reporting which notoriously underestimates the actual food intake. Furthermore, sham surgeries are not feasible in

humans. Rodent (and other) models do not have these limitations and are thus indispensable in the study of natural ingestive behaviour after surgery.

Given these limitations in human studies, data from mainly RYGB patients demonstrate very large reductions in energy intake (compared with pre-surgical levels) of about -55% (-47 to -66%) at 6 months and about -40% (-19 to -49%) at 2–3 years (4,27–30). Energy intake for the earlier post-surgical period may be even lower with around -70% to -80% (4,31) and reduced energy intake appears to last almost indefinitely, with a reported reduction of -21% at 10 years across all types of surgery (27). Even though energy intake is not corrected for the substantial weight loss, it appears to be the major contributor to weight loss and prevention of weight regain.

Fecal energy loss because of malabsorption can additionally reduce metabolizable energy. Although a number of rodent studies report no significant fecal energy loss, a majority of human and a few rodent studies do find significant malabsorption particularly of fat. In one human study, the efficiency of fat absorption significantly decreased from 92% before surgery to 72% at 5 months and 68% at 14 months after RYGB, translating into losses of 124 and 172 kcal d⁻¹ (32). Based on parallel measurements of energy intake, the study concluded that malabsorption accounted for about 6% at 5 months and 11% at 14 months of the total reduction of metabolizable energy intake (32). Thus, while not negligible, the contribution of malabsorption to the total energy balance is relatively small compared with the reduction in energy intake.

Weight maintenance/regain phase

Existing long-term data on energy intake after RYGB and other bariatric surgeries suggest fundamental differences between humans and rodents, particularly mice. While human studies show continued suppression of energy intake at 2 years and later after RYGB (4,27–29,33), food intake suppression in rats and mice typically lasts only for about 2–4 weeks after surgery (9,34–36). The suppression of food intake in various rat models of RYGB is highly variable, with no changes or even slight increases in food intake even at early time points (37), to lasting, although moderate, suppression for up to 10 months (38). In the few viable mouse models described, initial suppression of food intake is even shorter than in rats and during the weight maintenance phase, it is typically not changed or slightly higher than in sham-operated controls (10,11,36,39).

In summary, energy intake and metabolizable energy are drastically reduced at least initially in both humans and rodents and are mainly responsible for the weight loss phase. It is not clear whether the more substantial and sustained reduction of food intake in humans is due to the same surgery-induced physiological factors responsible for

the early suppression in rodents or the effects of the rigorous behavioural coaching before and after surgery. However, it is becoming clear that this drastic reduction in energy intake and its consequences on body weight are mainly responsible for the rapid improvement of glycaemic control and resolution of diabetes. Therefore, the acute hypocaloric state during the initial weight loss phase is an important research target to understand its underlying mechanisms. Feeding the same low-caloric diet ingested by RYGB patients to non-surgical control subjects results in rapid body weight loss. In one recent study, RYGB patients and non-surgical control obese subjects provided with 500 kcal d⁻¹ of a liquid diet with a macronutrient content similar to that consumed by patients after RYGB for the first 21 d after surgery lost 8.1 and 7.2%, respectively, of their pre-surgical body weight, with similar significant improvements of glycaemic control (41). In another study, RYGB surgery patients were subjected to the same very-low-calorie (~ 1700 kcal per 7 d) dietary regimen for 1 week before surgery and after surgery with a washout period in between. Surprisingly, weight loss with the diet alone was significantly larger than with diet plus surgery (5.1 vs. 2.9%) and again, there were similar significant improvements in glycaemic control (42). Together with other short-term controlled studies (43,44), these findings strongly suggest that reduced energy intake after RYGB leads to a profound hypocaloric state followed by rapid weight loss that fully explains the rapid improvements in glycaemic control.

If the initial reduction of food intake and weight loss is one key effect of bariatric surgery, maintenance and defence of this reduced body weight level is the other one. This is in stark contrast to caloric restriction-induced weight loss, which is followed by hyperphagia and prompt weight regain, even if pre-intervention weight was in the obese range. Successful bariatric surgery and particularly RYGB appears to neutralize the powerful counter-regulatory mechanisms that are engaged by weight loss. The major counter-regulatory response to weight loss, increased hunger, seems to be offset or defused after RYGB. Why do RYGB patients not return to pre-surgical levels of food intake to regain preoperative body weight? Why do rodents not become hyperphagic to regain preoperative body weight?

Mechanisms of reduced food intake

Ingestive behaviour is ultimately controlled by the brain, but this says little about the information used by the brain for making the decision to eat or not to eat. This information can be derived from internal as well as external signals and signal processing can take place outside or inside awareness. For example, low leptin levels and previously rewarded food cues from the environment can both induce

strong feelings of hunger and initiate ingestion. The strong hunger drive induced by fasting and starvation occurs mainly in the absence of awareness and at least partially bypasses human executive control, while much of the regular daily food intake initiation and meal size is largely under executive control. The former system is also known as homeostatic regulator of energy balance with key components in the hypothalamus-brain stem axis. This is the system that defends an optimal level of body weight/adiposity for a given individual and environment by engaging hormonal and neural feedback mechanisms controlling the major effectors of energy intake and expenditure (45). The latter is often referred to as non-homeostatic or hedonic system with key components in the limbic system and cortex. Importantly, both systems are highly interactive so that internal signals can modulate hedonic systems in a bottom-up fashion and hedonic as well as cognitive processing can override homeostatic functions in a top-down fashion (46). It is within this framework that we discuss the potential mechanisms by which bariatric surgery suppresses food intake and reduces body weight.

Does bariatric surgery change the homeostatically defended body weight level?

Defence of a set-point is indicated behaviourally when perturbed body weight (either downwards or upwards) promptly returns to its pre-perturbation level. There is now considerable evidence that rodents after bariatric surgery also defend their 'new' body weight this way. If rats with sleeve gastrectomy are exposed to additional exogenous food restriction to further lower their body weight, they rapidly return to their original body weight when unlimited food access resumes (47). Similarly, elevated food intake and body weight in RYGB rats, achieved with blockade of central melanocortin-3/4 receptor signalling, promptly return to their original (low) body weight when the blockade is removed (manuscript under review). Furthermore, female rats with sleeve gastrectomy increase body weight when pregnant and return to pre-pregnancy body weight after delivery (48). In all these cases, rats are able to easily double food intake despite their surgical intervention, demonstrating their physical ability to eat more and highlighting that they chose to eat less and defend a lower body weight (49). The neural mechanisms of set-point regulation are far from completely understood and there is no convenient measure to demonstrate the neurological correlate of regulation (for more in-depth discussions see (50–53)). The mechanisms by which RYGB offsets increased hunger is perhaps the most crucial question for translational research ultimately directed towards non-surgical therapies. A recent neuroimaging study, which examined neural responses to visual food stimuli throughout the brain in severely obese and normal-weight women as well as in

women 4 years after RYGB, may provide an important clue (54). All the significant differences in neural activity, including the diminished response to high-calorie food pictures in the hypothalamus between obese and normal weight subjects were normalized in RYGB patients. Importantly, because visual analog ratings of hunger were significantly lower and ratings of satiety were higher in RYGB patients compared with both other groups, these findings could be interpreted as evidence for a changed set-point, although they do not provide any clue as to the specific hypothalamic mechanism involved.

The expression level of the basomedial hypothalamic peptides AGRP/NPY and POMC/CART has often been used as a read-out for the homeostatic regulator because of the strong anabolic and catabolic effects of manipulating these neurons. Increased AGRP/NPY expression and/or decreased POMC expression indicate an energy depleted or 'hungry' state as seen after prolonged food deprivation (55). Therefore, if this same pattern of gene expression is observed after surgery-induced weight loss, it would indicate that the subject is metabolically 'hungry' and if the expression levels are unchanged, it would indicate that the subject is 'satisfied' with the metabolic state. As recently reviewed (56), the few studies addressing this question provide conflicting results with changes in both directions (34,57–59). Future studies should measure gene expression at different time points after surgery and after a meal to obtain a more definitive answer.

Under normal healthy conditions, leptin is a master regulator of this hypothalamic yin and yang system. Most importantly, any decrease of circulating leptin or leptin signalling in the basomedial hypothalamus strongly stimulates AGRP/NPY gene expression and neuronal activity and inhibits POMC/CART gene expression and neuronal activity, a pattern that leads to increased hunger and reduced EE and guarantees energy sufficiency. However, in obese humans and animals, circulating leptin is dramatically increased in proportion to the amount of body fat, but because of cellular leptin resistance, it is unable to generate a catabolic state that would lead to weight loss. Because calorie restriction-induced weight loss in obese subjects has been demonstrated to resensitize leptin action (60), it is conceivable that bariatric surgery-induced weight loss has a similar effect. However, in a recent direct test of this hypothesis, administration of leptin failed to reduce body weight further in RYGB patients (61), suggesting that the incomplete reversal of obesity from a body mass index of ~48 to ~34 was not enough to restore leptin sensitivity. A similar conclusion was reached in a study after vertical sleeve gastrectomy in rats (34).

Finally, the involvement of an energy balance regulator in the basomedial hypothalamus can also be measured in downstream signalling effects through melanocortin receptors. Similar to the inconsistent evidence for AGRP/NPY

and POMC/CART expression levels discussed earlier, studies in melanocortin-4 receptor (MC4R) knockout mice provide inconsistent results. In RYGB mice, weight loss requires MC4R (36,62), while vertical sleeve gastrectomy (VSG) rats show body weight loss independent of MC4R (63). Human studies in subjects with heterozygous MC4R mutations showed that gastric banding and sleeve gastrectomy were equally effective in reducing body weight (63,64), while another study showed that gastric banding was less effective (65). In a patient with complete functional loss of both alleles of the MC4R, adjustable gastric banding did not result in long-term weight loss (66). One reason for the conflicting results may lie in the redundancy of homeostatic feeding circuitry, which was at least demonstrated for AGRP neurons. AGRP neurons coexpress the inhibitory acting neurotransmitter GABA and the orexigenic acting NPY. Deletion of all these components in AGRP neurons showed robust effects on feeding behaviour, while monogenic deletions had no effect on feeding behaviour because each of these components can compensate for each other (67).

In summary, although behavioural evidence shows that after RYGB and sleeve gastrectomy rodents appear to defend a new lower body weight set-point, there is not much consistent evidence for an involvement of leptin-sensitive basomedial hypothalamic AGRP/NPY and POMC/CART neurons and their downstream signalling pathways in establishing this new set-point. However, because of the crucial role of this circuitry in energy balance, its potential role should be further pursued. The ob/ob and db/db mouse models as well as assessments of molecular determinants of leptin receptor signalling such as the induction of phospho-

signal transducer and activator of transcription 3 (STAT3), phospho-tyrosine protein phosphatase 1B (PTB1B) and suppressor of cytokine signaling 3 (SOCS3) in relevant brain areas should be helpful in future studies.

Does bariatric surgery change food hedonics?

The ability to engage in survival promoting behaviours such as ingestive behaviour is a fundamental evolutionary mechanism critically guided by the so-called brain reward system. A considerable body of evidence has accumulated demonstrating differences in structure and function of the brain reward system between lean and obese humans and rodents (see (68–70) for comprehensive reviews). An important question in defining the relationship between food reward and obesity is what comes first – are differences in reward functions driving development of obesity or is the obese state impairing reward functions? Bariatric surgery patients are a valuable resource for studying this question.

Bariatric surgery changes food choice

Many human and rodent studies report changes in food preferences and choice and most of the earlier findings were recently reviewed (71–73) (Table 2). The most commonly observed effect in humans is a shift from overly sweet and fatty energy-dense foods to less energy-dense foods (74). Several rodent studies find a shift from a very high preference for high-fat diets before surgery and in the obese state towards lower preference of such diets after both RYGB and sleeve gastrectomy in longer-term two- or three-choice paradigms (35,38,75–77). However, the underlying mechanisms for these changes, both with regard to the specific

Table 2 Similarities and differences in measurements of food hedonics after bariatric surgeries in humans and rodent models

	Human	Rodent
Food Hedonics	Intake of calorically dense versus less dense foods	↓ ~12% at 16 d after RYGB in rats (35) ↓ ~24, 24 and 27% at days 22–40, 41–80 and 81–150 after RYGB in rats, respectively (38) ↓ 5 weeks after VSG in rats (75) No differences after VSG, ↓ after RYGB in rats at 8 weeks (76) ↓ 10 d after RYGB in rats (77)
	Changes in taste sensitivity	NA
	Changes in taste preference	↓ in taste preference for sucrose after RYGB in rats (80,82,83)
	Changes in 'liking'	↓ liking of high versus low-calorie foods (concentrations of sucrose or corn oil) after RYGB in rats (88)
	Changes in 'wanting'	↑ wanting of high-fat foods in diet-induced obesity rats after RYGB (88)
	↑ sour and bitter stimuli, ↓ sweet and salty after RYGB (78) ↑ sweet stimuli after RYGB (79,80) ↓ sweet stimuli after RYGB (81)	
	No difference in sweet taste preference after RYGB (80) ↓ in taste preference for sucrose after RYGB (81)	
	↓ liking of high versus low-calorie foods after RYGB (100)	
	↓ wanting of high versus low-calorie foods after RYGB (94,96,100) No difference in wanting of high-fat foods after RYGB (95)	

NA, not applicable; RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy.

neural components involved and the mediating signals from the gut or other organs, are not well understood.

Changes in taste sensitivity and preference

There is a growing number of studies investigating whether post-operative changes in taste perception following RYGB may influence eating behaviour and by extension weight loss. Taste perception is classically broken into two components, taste acuity (sensitivity) and taste preference or palatability (hedonic value). Clinical and basic researchers alike have ventured to address if indeed RYGB augments one or both of these classic components of taste perception. The earliest work in this area was conducted by Scruggs *et al.*, who examined changes in taste acuity for sweet, salty, sour and bitter stimuli in patients that were to undergo RYGB for clinically severe obesity (78). They found a significant up-regulation of taste detection and recognition of sour and bitter stimuli in post-operative RYGB patients. At the same time, patients exhibited a trend towards a reduction in the detection and recognition of sweet and salty stimuli. Three subsequent investigations into taste acuity also found that RYGB appeared to modify patient's detection and recognition of sweet stimuli, particularly sucrose. However, these studies did not find significant changes in patient's taste perception of other stimuli following RYGB and, in fact, did not reach a consensus of whether RYGB significantly increased (79,80) or decreased (81) sucrose taste sensitivity. Examinations of taste preference in these studies also produced discordant findings. Bueter *et al.* concluded that changes in taste sensitivity did not affect the hedonic value of sucrose (80), while Pepino *et al.* found that RYGB patients shifted their responses to repeated sucrose exposure from pleasant to unpleasant during post-operative palatability trials (81). Interestingly, Pepino *et al.* observed a threefold decrease in lingual fungiform papillae gene expression of α -gustducin in patients who underwent RYGB, which may explain their reduced taste sensitivity to sucrose (81). Taken together, the clinical literature would suggest that RYGB alters patient's taste perception of sucrose.

Moving from the bedside to the bench top, multiple lines of basic research evidence also support a post-operative shift in the taste perception of sucrose and other sweet stimuli. Tichansky *et al.* examined a Sprague Dawley rat model of RYGB for changes in sweet taste behaviour and found a decreased sensitivity or preference for sucrose (82). This data nicely complemented that of Bueter *et al.*, who observed a drop in post-operative sucrose intake in a Wistar rat model of RYGB with a two-bottle choice challenge (80). These authors also noted decreased alimentary limb expression of T1R2 and T1R3 receptors along with increased plasma GLP-1. One tantalizing possibility, given the close relationship between T1R receptors, α -gustducin

and GLP-1, is that the elevated circulating GLP-1 that accompanies RYGB may influence T1R-related signalling pathways that are crucial for peripheral sweet taste perception (80). Another study, from Hajnal *et al.*, addressed whether RYGB altered the central nervous system circuits governing sucrose taste perception. In addition to confirming reduced sweet taste acuity or preference with a two-bottle choice challenge, these authors also found post-operative decreases in pontine parabrachial nucleus (PBN) neural responses to sucrose in two rat models of RYGB (83). Although the emerging picture is complex, it seems that both peripheral and central taste processing of sweet stimuli may be altered by RYGB. It would seem that one component of taste perception is not necessarily dependent on the other and that both components may be independently affected by RYGB. Future studies are needed to determine exactly how altered taste processing of sweet stimuli may inform food selection, which may contribute to patients consuming a lower calorie diet and weight loss.

Changes in hedonic value of specific foods ('liking')

The food reward system is a complex neural system that can be divided both anatomically and operationally into several components. One plausible and influential operational differentiation has been to distinguish hedonic liking from wanting and learning as suggested by Berridge and Robinson (84). This distinction is based on the simple facts that a food item that is liked is not necessarily wanted at a given time and that learning is necessary to predict the reward value of a given food. Unfortunately, the three operational components do not simply segregate into three anatomically distinct neural circuits, but whereas 'liking' of food is mainly organized by relevant sensory pathways such as olfaction, taste and vision, as well as their corticolimbic representations, 'wanting' is mainly organized by the mesolimbic dopamine system consisting of midbrain, basal ganglia, cortex and hypothalamus. For reward-related learning, the interaction of these above-mentioned pathways is further enhanced by additional cortical and subcortical structures.

In rodents, implicit 'liking' of specific taste stimuli can be assessed by the taste reactivity test (85,86) and by the brief access lick test (87). Compared with high-fat diet-induced obese rats which 'like' high concentrations of sucrose and corn oil the most, rats after RYGB shift 'liking' from higher to lower concentrations of both sucrose and corn oil solutions, behaving similarly to lean rats (88). However, because weight loss of similar magnitude induced by calorie restriction led to the same shift, the mechanism appears to depend on weight loss rather than some other effect of the surgery (88). In humans, explicit liking can be assessed by questionnaire and visual analog scale (89). Similar to the findings in rats, RYGB patients preferentially

reduced liking of high- versus low-calorie foods as assessed before and after surgery (90). However, because no calorie restriction-induced weight loss group was compared, the mechanism(s) for this change remain unclear.

Changes in motivation to eat specific foods ('wanting')

In humans, motivation to eat has been assessed either by questionnaire or by actual measurement of how much an individual will work to obtain a food reward (91–93). When asked how much they want to eat foods that are directly in front of them or represented by pictures, RYGB patients show markedly decreased desire to eat (wanting) compared with before surgery (94), particularly if the food items are high in calories (90). Similar findings were obtained with assessment of food craving in RYGB patients compared with normal-weight controls, except that in contrast to most other studies, craving for high-fat foods was not different (95).

The willingness to 'work' for a food reward by pressing a computer key on a progressive ratio scale was recently tested in obese gastric bypass patients both before and after surgery and in normal-weight controls. The break point, a measure of wanting, was selectively decreased only in RYGB patients after surgery and only when they 'worked' for candy but not for vegetables (96). In RYGB rats, the willingness to work for a food reward (fruit loop) was assessed in the running alley, in which completion time for running from start to goal box is a measure of implicit 'wanting' (97). Surprisingly, and in stark contrast to the study in humans, 'wanting' was significantly lower in high-fat diet-induced obese versus lean rats and this impairment was completely normalized in rats 5 months after RYGB (88). One possible explanation for the discrepancy is the highly different 'work load' used – key pad presses in human subjects versus running in rats, and more research is needed to clarify the role of effort in motivated behaviours (98).

Looking for potential neural mechanisms that underlie changes in 'wanting', particularly changes in activation of components of the mesolimbic dopamine system, there is a growing literature employing functional magnetic resonance imaging and positron emission tomography neuroimaging as well as magnetoencephalography. The typical experimental paradigm consists in the presentation of food and non-food pictures, and in one study, direct oral stimulation while lying in the magnet. In normal-weight individuals, these visual and gustatory appetitive stimuli elicit characteristic patterns of increased neural activity in areas related to sensory processing as well as key areas of the mesolimbic dopamine system such as the ventral tegmental area, ventral striatum and various cortical areas. These responses are typically exaggerated in obese subjects and decreased after bariatric surgery (40,54,99–102), suggesting that external food cues lose

their ability to drive eating after surgery. Specifically, the decreased striatal activity observed in fasted RYGB subjects correlated with reductions in 'wanting' calorie-dense foods, but not 'liking' for such foods (90), reinforcing the idea of distinct neural systems mediating wanting and liking. Dopamine signalling through D1 and D2 receptors within target areas of the mesolimbic dopamine system is thought to be crucial for motivated behaviours such as food intake (103) and a few studies have begun to examine components of dopamine receptor signalling after gastric bypass surgery in humans and rats (104–106).

In summary, the initial sketchy reports of changes in acceptance of, and preference for, specific foods in bariatric surgery patients have now been largely confirmed in easier to control rodent studies. Specifically, a number of studies in rodents show decreased preference for sweet and fatty foods after RYGB or sleeve gastrectomy. Studies designed to identify the neural component(s) responsible for these adaptive changes further suggest that 'liking' of, not only high-fat, but also high-sucrose taste stimuli, is decreased after RYGB. However, whether this shift towards low-calorie sweet and fatty stimuli is due to changes in taste perception or more central components of taste processing is not yet clear and needs further investigation. Similarly, although one recent study found RYGB patients to be less willing to work for high-calorie food, there is no clear consensus regarding changes in the motivation to obtain food rewards ('wanting') and its underlying mesolimbic dopamine system.

Importantly, the mechanisms responsible for any changes in these components of food hedonics after bariatric surgery are not known. Candidate mechanisms include changes in signalling by gut hormones and other gut factors such as GLP-1, PYY, ghrelin, bile acids and microbiota-derived proteins, as well as changes in leptin signalling. None of these hypothesized mechanisms have been directly tested in interventional approaches, but the recent observations that both RYGB and sleeve gastrectomy are effective in reducing food intake and body weight in whole body knockout mice deficient in GLP-1 receptor (35) or ghrelin signalling (107) have somewhat shortened this list of important candidate mechanisms. Just as recently shown for improvements of glycaemic control (41), it is likely that surgery-induced calorie restriction and weight loss are perhaps more important than gut-specific hormonal mechanisms.

Ideally, future studies should be longitudinal, allowing assessment of food hedonism in the same subjects before surgery (in the obese state) and at several time points after surgery. It should also include matched, calorie restriction-induced weight loss groups for comparison and food hedonics should be tested in both fasted and fed conditions to capture the full dynamic range.

The role of aversive learning and conditioned anorexia

The marked changes in ingestive behaviour with smaller meals and shifts in preference observed in humans and rodents after RYGB (28,38,72,74,77,88,108) strongly suggest the involvement of coping or learning mechanisms to avoid unpleasant gastrointestinal sensations such as fullness, nausea and pain when ingesting too much of certain foods. Indeed, bariatric surgery in humans often causes episodes of fullness, nausea, pain and vomiting with different intensity and frequency for different bariatric procedures (109–113). Furthermore, conditioned taste aversion to orally administered corn oil was demonstrated in rats after RYGB (77).

The physiological states and mechanisms of satiety and nausea are typically discussed as distinct, even though they are mediated by partially overlapping brain areas including the nucleus of the solitary tract, parabrachial nucleus (PBN) and amygdala (114–119) (and see (120) for a recent review). Earlier literature has identified the PBN as a site of integration of viscerosensory information, including gastric distension and taste (115,116,121). The PBN, particularly its lateral subnuclei, is activated by a number of diverse stimuli including intraperitoneal administration of the satiety hormones CCK-8 (122), GLP-1 (117,123), Exendin-4 (124), PYY (118) and amylin (117,125), electrical stimulation of vagal afferents (126), the 5-HT reuptake inhibitor dexfenfluramine (122), systemic administration of LiCl (119,127), lipopolysaccharide (LPS) (128) and other immune-activation signals (129), and the cancer chemotherapy drug cisplatin (130,131). Importantly, a common effect of all these challenges is a reduction of food intake. Thus, there is a strong correlation between lateral parabrachial nucleus (LPBN) activity and anorexia.

Only recently has a more integrative picture emerged, with satiety, nausea and anorexia seen as a functional continuum that opposes hunger orchestrated by hypothalamic AGRP/NPY neurons. More specifically, a group of calcitonin gene-related peptide expressing neurons has been identified in the external lateral subnucleus of the PBN (132–137). The profound anorexia and starvation of mice after AGRP neuron ablation in adult mice is surprisingly not only caused by food intake stimulatory actions of AGRP and NPY projections elsewhere (138–140), but also by withdrawal of GABA_Aergic inhibitory input to these critical lateral PBN neurons. Activity within this specific group of neurons is positively correlated with the food intake-suppressing effect of a variety of stimuli such as exogenous cholecystokinin and amylin, lithium chloride and LPS (136), and we recently found similarly exaggerated neural activity in these neurons in mice eating a high-fat meal after RYGB as compared with sham surgery (Berthoud, unpublished observations). These preliminary

observations suggest that the LPBN anorexia pathway is strongly activated by eating a meal, particularly a high-fat meal, early after RYGB, potentially explaining the rapid behavioural change of eating smaller but more frequent meals which is evident soon after surgery (38). It is conceivable that this exaggerated activation leads to negative reinforcement of eating large meals and may be selective for specific food types, e.g. high-fat diet (75,88,96). This could lead to permanent changes in food intake through plastic neural changes within the anorexia pathway and its interactions with the homeostatic regulator and the reward system.

In summary, there is clear evidence that ingestive behaviour and food choice changes after bariatric surgeries and that eating 'as usual' can cause discomfort and nausea. It is thus very plausible that animals and humans learn to avoid these negative consequences and thereby reduce food intake. The recent rediscovery of the lateral PBN as a hub of viscerosensory integration and the molecular identification of its major inputs and outputs offer the intriguing possibility that this anorexia pathway plays a crucial role in the food intake-suppressing effects of bariatric surgeries. This idea gains additional support from the demonstration that this anorexia pathway is part of the classic homeostatic feeding circuits in the basomedial hypothalamus and projects to important behavioural effector systems in the paraventricular nucleus of the hypothalamus and the mesolimbic dopamine pathways. It may thus be possible to leverage this system for the development of drug or behavioural therapies to suppress food intake without induction of nausea.

The role of executive control

When bariatric surgery patients are asked to describe their eating experience using interpretative phenomenological analysis, self-control was the central theme permeating all areas of the interviews (141,142). Most of these patients have been struggling all their life with control over eating and successful surgery appeared to make control easier. Ogden *et al.* concluded that successful surgery without weight regain brings the patient's mind 'in gear', while failed surgery is characterized by a continuing battle for control (142). While the liking and wanting systems generate incentive salience and craving (as discussed earlier), the executive control system acts as a brake to align impulsive behaviour with longer-term goals. Inhibitory control is particularly important to resist temptation to eat as stimulated by ubiquitous food cues in the modern environment.

The neural system underlying executive control is not well-defined, but the dorsolateral prefrontal cortex (DLPFC) is thought to be an important component (143–146). Very little is known about how these executive control functions impact obesity or how it may change

after RYGB. A recent study by Goldman *et al.* may be among the first to address these questions (147). These authors initially stratified a population of recent RYGB patients based solely on how successful they were at weight loss and then compared their neural responses with food cues during an executive control challenge. This challenge consisted of two parts, a crave phase in which patients were told to let themselves desire a given food after seeing its visual cue and a resist phase in which they were told to do the opposite. Functional magnetic resonance imaging analysis of patients' brains revealed that the crave phase was associated with dorsomedial prefrontal cortex (DMPFC) activity and the resist phase was associated with DLPFC activity. While their entire RYGB patient population had similar levels of DMPFC activity during the crave phase, the most successful weight loss patients demonstrated significantly higher DLPFC activity during the resist phase. It would appear then that the success of RYGB surgery may be due, in part, to the post-operative ability of an individual to mobilize neural circuits involved in executive control (148).

It is unclear if executive functions are specifically impaired with obesity or preoperatively in RYGB patients. The extent to which the hedonic value of a given food cue impacts executive control functions also remains to be determined. That is to say, RYGB post-operative changes in food hedonics may also facilitate executive control functions (90). If this is the case, then by simply removing or reducing the hedonic value of notoriously high-calorie foods through RYGB would make it easier to self-regulate their intake. Another intriguing possibility is that the ability to mobilize DLPFC activity is aided by signals from the PBN-amygdala anorexia pathway as discussed earlier.

Summary and conclusions

During the past decade or so, there has been a surge in studies characterizing the effects of bariatric surgeries in humans and rodents. They have demonstrated numerous structural, functional and molecular changes in the gut, the brain and the other organs as well as changes in energy metabolism, glucose homeostasis and behaviour. After going for the 'low-hanging fruit', it is now time to separate irrelevant changes from mechanistically relevant ones. The marked and sustained body weight loss and concomitant correction of many obesity-related impairments in metabolism and behaviour are well-documented, while other effects that do not depend on the hypocaloric state and weight loss are variable and less clear. In general, while the sustained body weight loss in humans is mainly explained by reduced energy intake, not increased EE, the opposite is true for rodents; only temporary reduction in energy intake but increased EE, at least in the long-term and particularly

in mice. However, regardless of these differences, a key observation is that energy intake is not increased to regain lost body weight, even though food intake can be doubled if properly stimulated. This suggests active defence of a new lower body weight level after surgery. Thus, explaining the potential mechanisms for this sustained relative hypophagia is perhaps most crucial for future non-surgical treatments of obesity. While a number of candidate mechanisms have been proposed on the basis of changes in gut hormone secretion as well as changes in peripheral and central targets of such hormones, direct testing of individual signalling cascades was unable to confirm any of these hypotheses so far.

Conflict of interest statement

The authors declare no conflict of interest.

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