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REVIEW

Does gastric bypass surgery change body weight set point?

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The relatively stable body weight during adulthood is attributed to a homeostatic regulatory mechanism residing in the brain which uses feedback from the body to control energy intake and expenditure. This mechanism guarantees that if perturbed up or down by design, body weight will return to pre-perturbation levels, defined as the defended level or set point. The fact that weight re-gain is common after dieting suggests that obese subjects defend a higher level of body weight. Thus, the set point for body weight is flexible and likely determined by the complex interaction of genetic, epigenetic and environmental factors. Unlike dieting, bariatric surgery does a much better job in producing sustained suppression of food intake and body weight, and an intensive search for the underlying mechanisms has started. Although one explanation for this lasting effect of particularly Roux-en-Y gastric bypass surgery (RYGB) is simple physical restriction due to the invasive surgery, a more exciting explanation is that the surgery physiologically reprograms the body weight defense mechanism. In this non-systematic review, we present behavioral evidence from our own and other studies that defended body weight is lowered after RYGB and sleeve gastrectomy. After these surgeries, rodents return to their preferred lower body weight if over- or underfed for a period of time, and the ability to drastically increase food intake during the anabolic phase strongly argues against the physical restriction hypothesis. However, the underlying mechanisms remain obscure. Although the mechanism involves central leptin and melanocortin signaling pathways, other peripheral signals such as gut hormones and their neural effector pathways likely contribute. Future research using both targeted and non-targeted 'omics' techniques in both humans and rodents as well as modern, genetically targeted, neuronal manipulation techniques in rodents will be necessary.

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INTRODUCTION

Gastric bypass and other bariatric surgeries are the most effective treatment option for obesity and its associated comorbidities such as diabetes, cardiovascular disease, sleep disturbances and certain cancers. Although serious complications can occur, most patients report significant improvements in general health and quality of life, and there is an intensive search for the mechanisms underlying these beneficial effects. A key observation is that the large weight loss after gastric bypass surgery does not seem to make patients hungrier and hypo-metabolic, responses typically seen after calorie restriction-induced weight loss. Instead, many gastric bypass patients seem both psychologically and physiologically 'at ease' with their reduced body weight. The surgery seems to have reprogrammed the defended body weight at a lower level. In this non-systematic review, we highlight recent observations in rodent models of bariatric surgery that support the notion of resetting the level of defended body weight and discuss potential underlying mechanisms.

BEHAVIORAL EVIDENCE FOR RYGB-INDUCED CHANGE IN DEFENDED BODY WEIGHT

Given the remarkable constancy of body weight over the adult lifespan, the concept of a homeostatically controlled body weight set point was introduced decades ago.[1,2] The basic concept is that a certain level of body weight (often referred to as the set point) is actively defended through a neural mechanism that uses feedback from the body to control energy intake and expenditure. Although the definition of set point has been debated over the years (for example, refs 3–5), it is now generally agreed that the set point is not 'set in stone', but rather is flexible and adaptable, taking into account essential biological and environmental circumstances such as pregnancy, season and long-term nutrient availability.[6] In this review, the terms 'set point' and 'level of defended body weight' are used interchangeably without implying a defined underlying mechanism.

Because bariatric surgeries result in drastic reductions of food intake and weight loss, it is a commonly held view that they at least partially restrict total food intake in a non-physiological way. When these surgeries were pioneered decades ago, simple physical restriction of food intake and some malabsorption may have been intended, but resetting the defended body weight to a lower level clearly is a more physiological and thus preferred mechanism. Defense of a certain body weight can be ascertained by observing the metabolic and behavioral reactions to experimental perturbations usually accomplished by transient over- or underfeeding.[7,8] In our rat model of RYGB,[9,10] we have used chronic intracerebroventricular infusion of the melanocortin receptor antagonist SHU9119 to stimulate food intake.[11] As shown earlier,[12] SHU9119 powerfully stimulates food intake and over a 2-week infusion period results in significant weight gain and obesity in normal, chow fed as well as high-fat fed rats,[11] reminiscent of rats and mice with MC4R deficiency.[13,14] Importantly, when the antagonist infusion was halted, rats gradually returned to their pre-infusion body weight, thus demonstrating the concept of defense of their lower body weight. We thus used this approach to test whether rats that had settled at a lower body weight about 3 months after RYGB surgery would show a similar

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behavior. Indeed, upon SHU9119 infusion, RYGB rats increased body weight to levels seen before surgery and slightly above that of sham-operated rats (Figure 1).[11] When infusion was stopped, they returned to the same low body weight before infusion, clearly demonstrating that this low body weight is actively defended and not the result of an imposed physical restriction. We preferred this approach over forced intragastric feeding that results in the same voluntary feeding suppression[7,8] because it is more powerful and less invasive. Consistent with our findings, transient hyperphagia and weight gain was also observed in female rats with sleeve gastrectomy during pregnancy and lactation.[15]

In our mouse RYGB model,[16,17] we used a different approach, in that we lowered pre-surgical body weight by calorie-restriction before RYGB surgery. After 12 weeks on high-fat diet, mice weighed about 35 g, 12 g of which was fat mass. After calorie restriction and before surgery, they weighed 26 g, with only 4 g of fat mass. Instead of losing weight, these mice gained weight and fat mass after surgery to plateau at about 30 g, with 8 g of fat mass (unpublished observations). These findings clearly demonstrate that RYGB surgery does not indiscriminately lower body weight level by physically limiting food intake. Rather, special circumstances are taken into account and lean body mass is defended. Furthermore, in a larger cohort of high-fat-fed mice, RYGB-induced weight as well as fat mass loss was positively correlated with pre-surgical body weight and fat mass. The fatter the animal was before surgery, the more fat mass was lost after surgery. In contrast, lean mass was completely conserved by the surgery.

In summary, our findings suggest that RYGB results in the establishment of a new level of defended body weight and adiposity. A similar conclusion was reached in a previous study with calorie-restriction in rats with sleeve gastrectomy.[18]

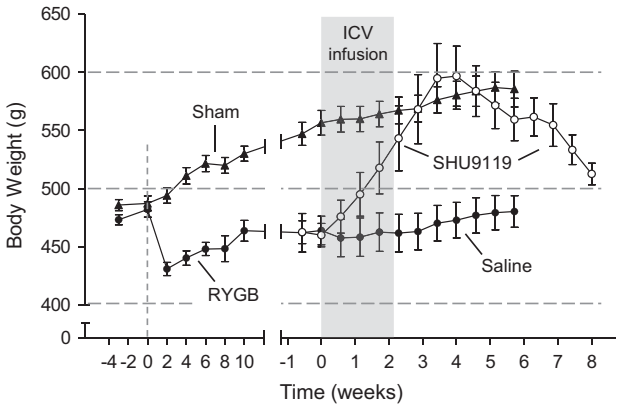

Figure 1. Behavioral demonstration of defense of reduced body weight level in rats with Roux-en-Y gastric (RYGB) bypass surgery. Rats that had reduced body weight after RYGB received infusion of saline or SHU9119, a potent melanocortin-4 receptor (MC4R) antagonist. MC4R blockade induced rapid weight gain to obese (sham-operated) body weight levels. After cessation of MC4R blockade body weight promptly returned to pre-infusion levels. Modified with permission from Mumphrey *et al.*,[11] copyright John Wiley.

Meal size is restricted after gastric bypass surgery

Meal pattern analysis in the above SHU9119-induced overfeeding study revealed different strategies to increase food intake in rats with RYGB vs sham surgery. Although sham rats increased meal size but not meal frequency, RYGB rats used the completely opposite strategy of increasing meal frequency but not meal size (Figure 2a). We had previously analyzed meal patterns in RYGB and sham-operated rats at an early and late time point after surgery with both liquid and solid food.[10] Two weeks after surgery, liquid (Ensure) meal size of RYGB rats was less than half that of sham-operated animals, while meal frequency was increased (Figure 2b). The decrease in meal size was entirely accounted for by the rate of eating, with no change in meal duration. Twenty weeks after surgery the difference in meal size had somewhat moderated (35% lower), but meal frequency was still twice as high in RYGB rats. Thus, our studies in rats indicate that although meal size and eating rate are restricted after RYGB, animals compensate by increasing meal frequency, resulting in an only slight or no reduction in total food intake.

In studies with bariatric surgery patients, it is standard procedure to provide a very low calorie diet for a week or two after gastric bypass surgery[19–21] and caloric intake is often also restricted before surgery. In addition, patients typically receive heavy dietary counseling before and after surgery, making it difficult to analyze quantity and pattern of voluntarily ingested food, particularly during the early post-surgical period. Nevertheless careful studies in patients from 6 weeks to 2 years after RYGB[22] revealed essentially similar effects on meal patterns as observed in our rats. RYGB patients show reduced meal size and a tendency for increased meal frequency, with decreased eating rate but maintained meal duration.[22] Also in agreement with our rat study, the effect on meal size and eating rate was strongest early after surgery and moderated somewhat later.[22]

In summary, studies in both rodent models and patients with RYGB clearly demonstrate changes in eating patterns indicative of major changes in appetite control mechanisms. RYGB clearly does restrict meal size and eating rate, particularly early after surgery. However, RYGB animals can increase total food intake if properly stimulated, and thus the weight loss is not simply due to a mechanical restriction of meal size. Mechanistically, it is highly likely that these are behavioral adaptations to avoid discomfort, nausea and pain generated by eating as usual.[22] It will be interesting to analyze the underlying adaptive neural mechanisms (aversive learning) for these dynamic interactions between the rearranged gut and the brain.

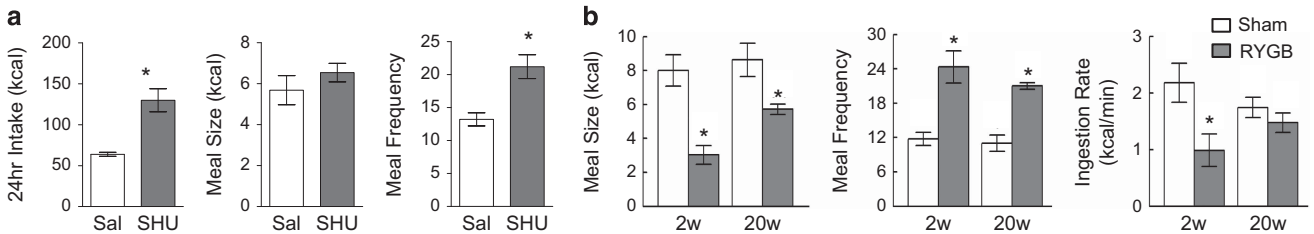

Figure 2. RYGB restricts meal size but not total food intake. (**a**) Total daily food intake, meal size and meal frequency of RYGB rats during 14-day ICV infusion of SHU9119. (**b**) Meal size, meal frequency and ingestion rate of liquid formula (Ensure) of rats at 2 weeks (2w) and 20 weeks (20w) after RYGB or sham surgery. *$P < 0.05$, RYGB vs Sham, *$P < 0.05$, SHU9119 vs Saline. Modified with permission from Zheng *et al.*,[10] copyright American Physiological Association.

POTENTIAL UNDERLYING MECHANISMS FOR CHANGE IN SET POINT

The multiple reciprocal signaling pathways between the gut and other organs and tissues that are potentially recruited in the effects of bariatric surgeries are depicted in Figure 3. Gut-to-brain communication through the circulation and neural connections is thought to be important, particularly for effects on eating and physical activity. However, communication with other organs that are important for energy and glucose homeostasis is also involved. In the following sections, mechanisms that have received the most attention will be discussed.

Role of leptin signaling

The discovery of leptin has provided an important missing link for the negative lipostatic feedback regulation of body weight, hypothesized long before by Kennedy.[1] It has become clear that leptin action on the hypothalamus is a major mechanism for the homeostatic control of body weight/adiposity.[23] In the absence of leptin signaling or after destruction of critical hypothalamic components of leptin signaling such as after VMH lesions, rodents and humans appear to regulate at a higher defended body weight.[24,25] It is thus possible that bariatric surgeries, particularly RYGB, change the defended body weight by restoring 'normal' leptin signaling and/or critical downstream signaling pathways in the hypothalamus and elsewhere. We have recently tested this hypothesis by carrying out RYGB surgery in leptin-deficient ob/ob mice.[26] Leptin-deficient mice lost significantly less body weight and fat mass after RYGB, compared with wild-type mice, but more than sham-operated mice (Figure 4a). Furthermore, leptin-treatment of RYGB mice led to exaggerated percent body weight loss in ob/ob compared with wild-type mice (Figure 4b), suggesting that normal leptin signaling has at least a partially permissive role for the full beneficial effects of RYGB on body weight.[26]

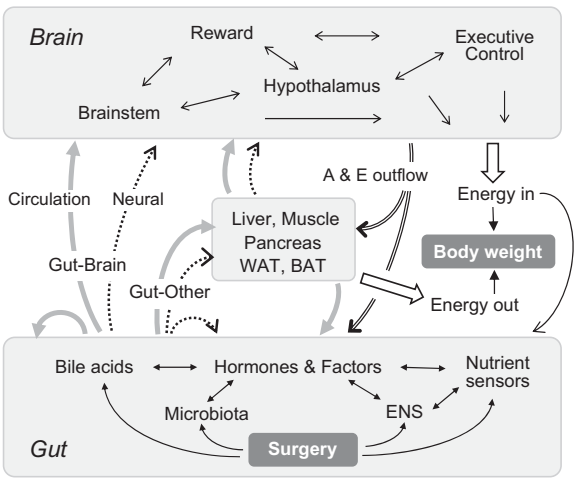

Figure 3. Schematic diagram showing the flow of information between the gut and the brain that is potentially important for the dynamically emerging beneficial effects of bariatric surgeries on body weight and glucose homeostasis. The primary impact of surgery leads to changes in gut structure and function that result in changes of humoral (solid gray lines and closed arrows) and neural (broken black lines and open arrows) signaling within the gut itself and to the brain and other organs such as liver, muscle, pancreas, white (WAT) and brown (BAT) adipose tissue. The secondary impact of surgery on these 'other' organs changes their signaling to the brain and back to the gut via humoral and neural mechanisms. The brain integrates humoral and neural signals from gut and other organs and orchestrates adaptive behavior and metabolic control through changes in eating behavior and autonomic/endocrine outflow (A & E outflow). Abbreviation: ENS, enteric nervous system.

However, it is not clear how RYGB-induced changes in leptin signaling lead to a lower defended body weight, as leptin levels rapidly decrease after the surgery, commensurate with the rapid weight loss. We therefore tested the possibility that RYGB reverses obesity-associated leptin resistance, making up for falling leptin levels, by measuring leptin-induced reduction of food intake and induction of phospho-STAT3 in the basomedial hypothalamus (Figure 5). Neither leptin-induced food intake suppression, nor leptin-induced pSTAT3 induction was augmented in RYGB mice compared with mice with sham surgery (Figure 5). Thus, increased leptin sensitivity is unlikely to be the mechanism for the beneficial effects of RYGB. This conclusion is corroborated by lack of increased leptin sensitivity after sleeve gastrectomy in rats[18] and after RYGB in humans[27] although intact leptin signaling is required for the full beneficial effects of RYGB in mice, the exact site and mechanism of leptin action remains to be investigated.

Although absence of leptin triggers a strong anabolic response and safeguards dangerous weight loss, increased leptin, even at high pharmacological doses, seems unable to trigger a catabolic response to safeguard weight gain. The existence of another circulating factor that stimulates catabolic mechanisms during states of overnutrition has recently been hypothesized.[28] Like leptin, this other factor may act on the hypothalamic circuit responsible for fine-tuning body weight homeostasis by differentially affecting energy intake and expenditure. Although this factor is distinct from leptin, it requires intact leptin signaling, as shown by the absence of food intake suppression following a period of intragastric overnutrition in leptin receptor-deficient Zucker rats.[8] Although normal rats intragastrically 'overfed' for 10 days progressively suppress voluntary food intake and exhibit complete anorexia for a few days following cessation of infusion, Zucker rats immediately return to pre-infusion food intake upon cessation.[8] It is thus possible that this factor has a role in the suppression of food intake and increase of energy expenditure after RYGB.

Fibroblast growth factor 21 (FGF21) could potentially fulfill the role of this unknown factor. FGF21 is primarily stimulated in adaptation to fasting,[29] particularly protein-restriction.[30] However, prolonged systemic infusion of FGF21 in the Siberian hamster, a model with seasonal body weight fluctuation, suppresses food intake and body weight and increases energy expenditure selectively during the high body weight phase (long days), but not during the low body weight phase (short days).[31] Furthermore, a single injection of antibodies to the FGF

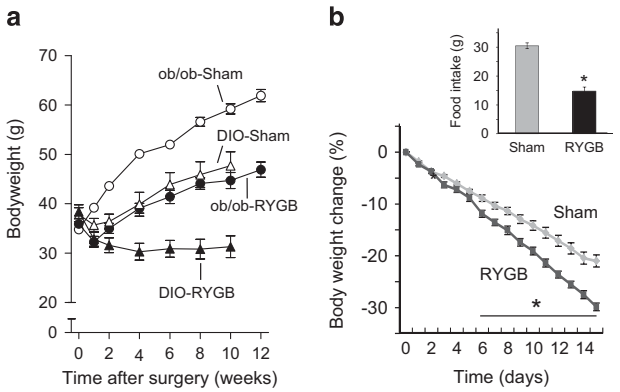

Figure 4. Partial attenuation of body weight-lowering effects of RYGB in leptin-deficient ob/ob mice. (**a**) Effect of RYGB (filled symbols) and sham surgery (open symbols) on body weight in genetically (ob/ob, circles) and diet-induced (triangles) obese mice. (**b**) Leptin treatment (daily injections of 1 mg kg^{-1}, i.p.) reduces body weight and food intake (inset) more in ob/ob mice with RYGB compared with sham surgery. *$P < 0.05$, RYGB vs sham. Modified with permission from Hao *et al.*[26]

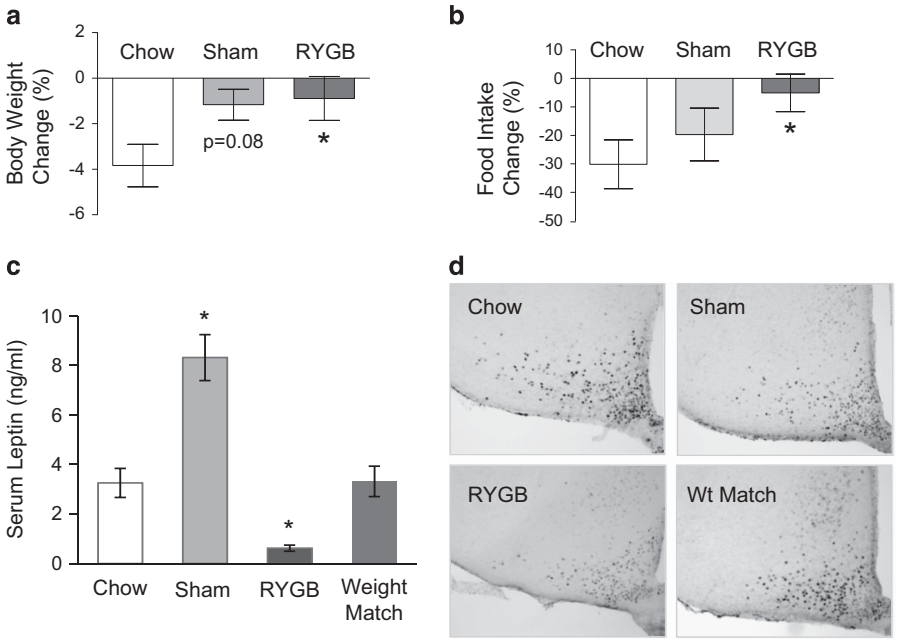

Figure 5. RYGB does not restore two measures of leptin sensitivity in mice. (**a**, **b**) Effect of 4-day leptin treatment (daily injections of 1 mg kg^{-1}, i.p.) on suppression of food intake and body weight in non-surgical mice fed chow (lean controls) and mice with RYGB or sham surgery fed high-fat (60% energy) diet. *$P < 0.05$ vs chow. (**c**) Serum leptin levels of non-surgical mice fed chow and mice with RYGB or sham surgery and non-surgical mice weight-matched to RYGB, all fed high-fat diet. *$P < 0.05$ vs chow. (**d**) Leptin-induced (1 mg kg^{-1}, i.p.) phosho-STAT3 expression in basomedial hypothalamus in non-surgical mice fed chow and mice with RYGB or sham surgery and non-surgical mice weight-matched to RYGB, all fed high-fat diet.

receptor-1c splice variant with dual agonist/antagonist activity produced a long-lasting suppression of food intake and body weight in diet-induced obese mice.[32] It will thus be interesting to test the potential role of FGF21 signaling in the beneficial effects of RYGB.

Role of melanocortin signaling

Melanocortin-4 receptor (MC4R) signaling is the most powerful catabolic downstream pathway of the basomedial hypothalamus, which is highly sensitive to signals of nutrient availability, including leptin. It is thus ideally positioned to mediate the catabolic effects of bariatric surgeries. The requirement of MC4R signaling to achieve reduced body weight with bariatric surgeries has been directly tested in MC4R-deficient rodents. One study concluded that MC4R signaling is not required for the full effects of sleeve gastrectomy in rats, because weight loss was identical in MC4R-deficient and wild-type rats.[14] However, interpretation was complicated by the fact that in this model of sleeve gastrectomy there is only a transient reduction of body weight, returning to pre-surgical levels already after 20–30 days and surpassing it by 25% at 10 weeks. The conclusion was entirely based on the higher body weight levels reached in sham-operated rats and ignored the massive weight regain of both genotypes after surgery.[14] Another study concluded that complete absence of MC4R signaling in homozygous, but not in heterozygous knockout mice, abrogated the effectiveness of RYGB.[33] Interpretation of that study is made difficult due to high mortality, low number of animals and the unusually low weight gain in MC4R-deficient mice, which was less than observed in other studies using homozygous MC4R-deficient mice.[34]

Using chronic pharmacological blockade of brain MC4R signaling 3–4 months after RYGB or sham surgery in rats (see Discussion above and Figure 1), we concluded that brain MC4R signaling is not the critical mechanism by which RYGB lowers defended body weight level.[11] However, interpretation of our findings was also not without problems. Although RYGB rats (that had plateaued at the lower body weight level) gained body weight during MC4R blockade, sham-operated rats showed an even stronger weight gain response. Thus, a final conclusion regarding requirement of MC4R signaling for the effects of bariatric surgeries in animal models is premature and additional studies will be necessary. In contrast to rodent models, studies in patients with heterozygous mutations at various loci are more consistent. With the exception of a few rare variants,[35] all studies looking at patients with MC4R variants found that gastric bypass surgery was fully effective.[14,33,35,36] However, gastric banding in one rare patient with complete loss of MC4R functionality did not produce a lasting reduction in body weight.

In summary, the most parsimonious conclusion from both rodent and human studies is that complete absence of MC4R signaling diminishes, but does not completely abolish, effectiveness of bariatric surgeries. However, the partial absence of MC4R signaling, due to heterozygous mutations, has relatively little influence on surgical outcome, even if it results in obesity before surgery. Thus, increased catabolic signaling through MC4R expressing effector pathways may be partly responsible for defense of a lower body weight level after bariatric surgery. It is interesting in this respect that basomedial hypothalamic mRNA expression levels of MC4R, as well as POMC and AGRP, the major MC4R ligands, were not altered at 10 and 35 days after sleeve gastrectomy.[18] Although this outcome suggests that the surgery-induced hypocaloric state and weight loss did not trigger the expected below set point counter-regulatory hypothalamic responses, there is no evidence that RYGB induces a permanent change in melanocortin signaling within the mediobasal hypothalamus. However, melanocortin signaling is not limited to the arcuate nucleus but extends to other hypothalamic and extra-hypothalamic sites. Specifically, MC4 receptors on preganglionic autonomic neurons are required for the full effects of RYGB on body weight reduction and increased energy expenditure.[37]

Role of extrahypothalamic mechanisms

Recent research has shown that feedback signals from the metabolic periphery such as leptin, GLP-1, ghrelin and insulin not only act on the hypothalamus and brainstem, but also on brain areas not classically associated with homeostatic regulation such as the mesolimbic dopamine system, sensory processing pathways and cortico-limbic structures (see Berthoud[38] for recent review). These extra-hypothalamic areas should be considered as part of a larger neural system regulating body weight homeostasis, one that takes into consideration environmental factors and their interaction with cognitive and emotional processes. Defended body weight may thus be determined by an interaction between the classical hypothalamic and these extra-hypothalamic brain areas in an environment-dependent manner, and bariatric surgeries may act on any component of this larger neural system. For instance, RYGB has been linked to changes in taste reactivity,[39–42] food reward[39,43,44] and cognitive functions,[45] which could all contribute to the mechanism defending a new body weight. However, before such conclusions can be substantiated, the nature and exact site of action of the mediating signals needs to be demonstrated in future experiments.

Role of gut hormones

Early experimental studies showing that infusion of blood from a donor rat with intestinal bypass surgery suppressed food intake in recipient control rats suggested increased secretion of a humoral factor after surgery.[46] Later studies in human subjects and rats after RYGB showed greatly increased meal-induced circulating levels of GLP-1[9,47–49] and PYY[9,47,50] as well as reduced levels of ghrelin,[9,50] and these gut hormones became prime candidate mechanisms for the beneficial effects of RYGB.[51] However, subsequent studies in rodents directly testing roles for each of these gut hormones in the beneficial effects of RYGB and sleeve gastrectomy were largely negative. Neither GLP-1 receptor deficiency nor ghrelin deficiency appreciably changed the effects of RYGB[17,52] or sleeve gastrectomy,[53,54] and neither GLP-1 receptor nor PYY/Y2 receptor blockade in the brain attenuated RYGB-induced body weight suppression[17] (but see Chandarana *et al*.[55] for a different outcome). Although these studies do not lend much support for individual roles of these hormones, it is possible that they act synergistically. Thus, the effect of RYGB may be mediated by the combined induction of multiple gut hormones and factors, such that removal of any single factor has little or no consequence. It is also possible that compensatory mechanisms shift control from the deficient signaling pathway to other hormones. Future experiments should thus use loss-of-function strategies that are either inducible and/or involve more than one signaling pathway. For example, because GLP-2 has been demonstrated to act in addition to GLP-1 on appetite in the brain[56] and the two hormones may substitute for each other, a double GLP-1R/GLP-2R knockout strategy may be necessary. This line of reasoning is supported by studies using octreotide, a non-specific inhibitor of all gut hormones.[51] Inhibiting postprandial gut hormone responses with octreotide normalized RYGB-induced reduction of appetite and food intake at least in the short term.[51]

Besides the L-cell hormones GLP-1 and PYY, other gut hormones and secreted factors such as neurotensin,[57] CCK,[58] ApoA-IV,[59] FGF 15/19[60] and bile acids[61–64] have been shown to be increased after RYGB and may thus be involved in mediating some of the beneficial effects of bariatric surgeries. The beneficial effects of sleeve gastrectomy have been demonstrated to require FXR signaling, an important target of bile acids.[65]

In summary, there is considerable indirect evidence for important roles of hormones and other factors secreted from the surgically rearranged gut in reducing energy intake in helping to implement a new, lower defended body weight. However, direct evidence from specific loss-of-function studies directed at single mechanisms or factors is still missing, at least for RYGB.

Role of microbiota–host interactions

The gut microbiome changes after gastric bypass surgery in humans,[66–68] rats[69] and mice,[70] and a recent transplant study in mice suggests that the changes in gut microbiome are responsible for at least some effects on body weight.[70] The signaling pathways leading from the microbiota in the intestinal lumen to reduced body weight are not known (Figure 3). One possibility is that microbiota-induced effects on intestinal barrier function reverse obesity-associated endotoxemia and inflammation.[71] Consistent with this idea is the observation of decreased paracellular permeability after gastric bypass in humans.[72] Reduced systemic inflammatory signaling could thereby lead to reduced inflammation of hypothalamic areas involved in set point regulation.[73] However, it is still not clearly understood which circulating inflammatory signals are involved and how they engage brain inflammatory processes. Another possibility is that the microbiota change bile acid profile and abundance which in turn signal through FXR and TGR5 receptors to peripheral organs involved in energy metabolism and to the brain. Finally, microbiota-derived factors such as neurotransmitters or neurotransmitter-like substances and other small circulating molecules may signal directly to the brain. This will require the full assessment of circulating metabolites of genomic and metagenomic origin by using global metabolomics approaches.

Role of neural communication pathways between the periphery and the brain

Besides the blood circulation, vagal afferents are in an ideal position to communicate information from the gut to the brain[74] and we have recently examined the role of this communication pathway in the body weight lowering effects of RYGB in rats. In the first study, eliminating vagal communication through the common hepatic branch, which innervates the liver, hepatic portal vein and the upper duodenum[75] had no effect on RYGB-induced reduction of food intake and body weight.[76] In the second study, eliminating vagal communication through the celiac branches that innervate most of the small and large intestines, including the Roux- and common limbs, attenuated RYGB-induced body weight loss by about 20%, consistent with increased vagal afferent signaling from these limbs.[77] A similar attenuation of RYGB-induced weight loss was observed with transection of the dorsal vagal para-esophageal bundle, which includes the celiac branches.[78] A recent clinical study in a large cohort of patients undergoing RYGB with or without vagotomy found no effect of vagotomy on percent extra weight loss.[79] However, because all these vagal lesions did not differentiate between afferents and efferents, the conclusions are limited and await more selective vagal manipulations such as targeted genetic deletions in mouse models of RYGB.[37,80]

CONCLUSIONS

Studies using forced over- or under-feeding paradigms in rodents clearly demonstrate defense of a new body weight set point after RYGB and sleeve gastrectomy, but the underlying mechanisms have not yet been fully revealed. Specifically, it is not clear what signals are generated in the re-arranged gut, how they reach the brain, and where exactly in the brain they act to evade a state of hunger and hypo-metabolism that is typically encountered with dieting-induced weight loss. Deletion of single factors hypothesized to be the critical surgery-induced signals has not yielded the expected results. Total absence of leptin and MC4R signaling seem to attenuate but not abolish the beneficial weight loss effects of RYGB, but partial loss of MC4R signaling has no effect, even

though it is obesogenic. Part of the complication in defining the critical brain circuitry is the recent realization that body weight homeostasis is not limited to parts of the hypothalamus, but includes other brain systems including sensory and corticolimbic systems, brainstem, and even autonomic outflow pathways.

CONFLICT OF INTEREST

H-RB has received lecture fees from Novo Nordisk, and grant support from the National Institutes of Health. CDM and HM have also received grant support from the National Institutes of Health. JY has received grant support from Suntory Foundation. The remaining authors declare no conflict of interest.

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