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J Clin Invest. 2015;125(3):939-948. <https://doi.org/10.1172/JCI76305>.

Review Series

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Roux-en-Y gastric bypass: effects on feeding behavior and underlying mechanisms

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Bariatric surgery is the most effective treatment for severe obesity, producing marked sustained weight loss with associated reduced morbidity and mortality. Roux-en-Y gastric bypass surgery (RYGBP), the most commonly performed procedure, was initially viewed as a hybrid restrictive-malabsorptive procedure. However, over the last decade, it has become apparent that alternative physiologic mechanisms underlie its beneficial effects. RYGBP-induced altered feeding behavior, including reduced appetite and changes in taste/food preferences, is now recognized as a key driver of the sustained postoperative weight loss. The brain ultimately determines feeding behavior, and here we review the mechanisms by which RYGBP may affect central appetite-regulating pathways.

Introduction

Increased caloric intake as a key driver of the obesity crisis. Epidemiological data suggest that increased ease of food accessibility over the last 30 years is the primary driver of the current obesity pandemic (1). It is clear, however, that population variation in body weight is heavily dependent on genetic susceptibility or heritable factors (2, 3). The majority of identified monogenic obesity arises from gene defects affecting the leptin/melanocortin pathway (4), placing this pathway at the center of energy balance control (Figure 1 and refs. 5, 6). Through a combination of experimental medicine and translational research, we now understand that hyperphagia is a consistent phenotype in patients with congenital leptin, leptin receptor, pro-opiomelanocortin (POMC) and melanocortin-4 receptor (MC4R) deficiencies, with strong genotype-phenotype correlations (4).

While monogenic causes of obesity illuminate the central pathways involved in the control of energy balance in humans, such mutations are rare and account for a small proportion of obesity in adults (4). Studies using a novel approach called genome-wide complex trait analysis have suggested that a multitude of common genetic variants, each with very small causal effects (7), could together account for 17% to 37% of the overall 35.0 k variance (8, 9). Polygene risk score based on 32 common variants with the largest effects on BMI, as identified in genome-wide association studies (10), are also predictive of severe obesity (11), suggesting that severe obesity represents an extreme of the population BMI distribution. The association of such polygene risk scores with obesity is strengthened with higher consumption of fried foods, highlighting the importance of gene-environment interactions (12). Of the SNPs associated with increased BMI, those in the first intron of the fat mass and obesity associated

(*FTO*) gene bear the strongest association with obesity and are strongly associated with extremes of obesity (13). Importantly, evidence to date suggests that the association between SNPs in *FTO* and BMI is predominantly driven by increased energy intake and not energy expenditure (14).

Brain imaging studies utilizing functional MRI (fMRI) and PET have provided insights into the role of obesity risk variants in modulating the neural response to food cues. For example, BMI-matched groups of obese patients with or without *MC4R* deficiency exhibited differential neural responses in key brain reward centers when viewing appetizing food images (15). In relation to common obesity risk alleles, a study incorporating fMRI with gut hormone measurement in *FTO*-locus genotyped subjects found that the *FTO*-linked obesity risk genotype affected neural responses to food cues in a ghrelin-dependent manner (16). Furthermore, fMRI studies have demonstrated altered activation in key areas of the brain reward system in obese patients compared with normal-weight control subjects (17). For example, increased activation of prefrontal and parahippocampal reward centers observed in obese individuals might theoretically lead to an increased motivation to acquire food (18). On the other hand, a more pronounced inhibition of specific reward centers, such as the dorsal striatum, in obese individuals compared with normal-weight control subjects (19) might result in blunted reward responses after eating palatable foods, with subsequent compensatory overeating. A recent fMRI study found stronger functional connectivity between brain areas involved in cognitive control, motivation, and reward in the fasted but not in the fed state in obese compared with lean women (20).

One hypothesis that provides a basis for these studies is that obesity may be characterized by a reward-deficiency state that involves reduced perception of the reward or hedonic value of food and resultant compensatory overeating (21). In support of this model, PET studies have demonstrated that lower striatal dopamine D2 receptor (D2R) availability is associated with higher BMI (22, 23). Supporting these findings, Guo et al. found

Conflict of interest: The authors have declared that no conflict of interest exists.

Reference information: *J Clin Invest*. 2015;125(3):939–948. doi:10.1172/JCI176305.

Figure 1. Schematic diagram illustrating the mechanisms involved in regulating feeding behavior. Nutrient entry into the GI tract causes stomach and intestine distension, secretion of pancreatic enzymes and bile acids, altered enteric and vagal nerve signaling, and exposure of gut enteroendocrine cells to nutrients, with altered circulating gut hormone levels (e.g., decrease in orexigenic hormone ghrelin and increase in anorectic hormones PYY3-36 and GLP-1). Gut-derived signals (nutrient, hormonal, and neural) and adipokines (e.g., leptin, IL-6, TNF- α , and adiponectin) act directly and indirectly upon brainstem and hypothalamic arcuate nuclei (first order neurons: orexigenic NPY/AgRP and anorexigenic POMC/CART). ARC neurons interact with second order neurons in the PVN, which influence the thyroid and adrenal hormonal axes, and in the LHA. Altered brainstem and hypothalamic activation influence brain reward and higher cognitive brain regions and together lead to altered feeding behavior. Abbreviations: ACTH, adrenocorticotrophic hormone; AgRP, agouti-related peptide; ARC, arcuate nucleus; AVP, vasopressin; CART, cocaine and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; ENS, enteric nervous system; FGF-19, fibroblast growth factor 19; LHA, lateral hypothalamic area; MSH, melanocortin-stimulating hormone; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; NT, neurotensin; OREX, orexin; OT, oxytocin; PVN, paraventricular nucleus; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; PNS, peripheral nervous system; SNS, sympathetic nervous system; ACTH, adrenocorticotrophic hormone, ENS, enteric nervous system.

ric surgery on a mass scale has sparked a whole new field of metabolic research that aims to develop a knifeless medical alternative to bariatric surgery (29).

Bariatric surgery is the most effective treatment for severe obesity, both in terms of weight loss achieved and maintained and with regard to amelioration of obesity-

not only a negative correlation between D2R availability and BMI in the ventromedial striatum, a region involved in attaching motivational importance to stimuli, but also a positive correlation between D2R availability and both BMI and opportunistic eating, in the dorsolateral striatum, a region thought to support habit formation (24). This study suggests that obesity may be characterized by both reduced perception of the reward aspect of food and habitual overeating.

Bariatric surgery

In light of multiple past failures of nonselective obesity pharmacotherapy (25), it is increasingly important to understand the biology of body weight regulation, in order to develop a more individualized approach to obesity therapy (26). Perhaps the most striking development in the obesity field in the last three decades has come not from bench-to-bedside research but from the operating theater (27, 28). The undeniable success of bariatric

related comorbidities (27, 30). In general, bariatric or “metabolic” surgery may be considered for the treatment of patients with BMI ≥ 40.0 kg/m² or with BMI ≥ 35.0 kg/m² plus comorbid conditions that will be improved by weight loss. In light of the aforementioned alterations in feeding behavior that are associated with obesity, it is imperative that we understand the effects of bariatric surgery on the drive to eat. Below we discuss the changes in and the potential mediators of feeding behavior induced by the exemplar bariatric procedure, the Roux-en-Y gastric bypass (RYGBP).

Changes in feeding behavior after RYGBP

RYGBP is the most frequently performed bariatric operation worldwide (47% of the approximate 341,000 procedures in 2011) (31) and leads to a long-term weight loss of about 20%–30% of body weight (32). RYGBP (Figure 2) alters the anatomy of the normal gastrointestinal (GI) tract with the formation of a small proximal gastric pouch to which a loop of mid-jejunum

is connected, creating alimentary, biliopancreatic, and common limbs. Thus, ingested nutrients bypass the majority of the stomach and upper small bowel (all of the duodenum and proximal jejunum) and directly enter the mid-jejunum, expediting delivery of nutrients to the distal gut. Consequently, nutrients, which pass through the alimentary limb, do not mix with pancreatic enzymes or bile acids, which pass through the biliopancreatic limb, until the common channel.

One of the most remarkable effects engendered by this procedure is the ability of RYGBP patients to maintain a markedly reduced body weight in the long-term after surgery (32). This concept is described as a resetting of the body weight set-point (29). The biological basis for the body weight set-point remains largely unknown, but central neural circuits are clearly implicated, given their role in determining feeding behavior (29). Weight loss achieved by dieting results in reductions in leptin secretion, which in combination with long-term gut hormonal adaptations (33) are thought to provide a strong physiological basis for the high failure rate of nonsurgical approaches to weight loss (34). As a consequence of these hormonal changes, the final effect of a diet is increased hunger and less satiety, leading to increased food intake and often complete regain of weight lost (34). Thus, dieting-induced weight loss is accompanied by an active “defense” of the higher body weight (34). Notably, in the case of RYGBP, the sustained body weight reduction occurs despite dramatic falls in circulating leptin levels (35). However, RYGBP-induced gut hormonal changes contrast strongly with those seen after dieting, as the former result in reduced hunger and more satiety, which lead to sustained weight loss (36). Thus, it has been postulated that altered humoral or neural signals, which originate in the gut and are transmitted to the brain, are responsible for the resetting of body weight set-point induced by RYGBP (Figure 2 and ref. 29).

Human observational studies

In 1980, soon after the inception of the intestinal bypass (IB), a forerunner of RYGBP, Bray and colleagues in a prescient paper (37) concluded that “food intake decreases in most, if not all, patients” after IB and postulated on oral (taste or smell), GI (mechanical distension or nutrient composition), and post-ingestional (nutrient or hormonal satiety mediators) factors that might mediate the reduction in food intake. Multiple studies in RYGBP patients have since highlighted how the reduced energy intake, typically on the order of 30%–50% caloric reduction, could be due to a combination of changes in appetite, meal patterns, and food preference (38). In addition, in studies employing the Power of Food Scale, which measures motivation to consume highly palatable foods, normalization of hedonic drive was observed in post-RYGBP patients compared with obese controls (39, 40). However, implications for actual consumptive behavior cannot be determined from these studies. The reduction in food intake after RYGBP is reflected in both smaller meal sizes and lower meal eating rates compared with preoperative measures (41). In general, these changes are found to persist in the long term postoperatively (41). There is, however, considerable variability in eating habits after RYGBP (42), the loss of control of which is closely associated with weight regain (42), which occurs in up to 20% of patients (32). In a comparison with weight loss-matched patients who underwent a purely restrictive

bariatric procedure, adjustable gastric banding (AGB), RYGBP patients appeared to exhibit a shift in sweetness palatability from pleasant to unpleasant (43). Similarly, RYGBP was again found to be associated with a shift in tastes from high reward value to low reward value in a study using a progressive task ratio paradigm (44). However, it remains unclear whether this shift in palatability actually affects eating behavior and food selection (43, 45). Recent studies suggest that emotional and uncontrolled eating are both decreased postoperatively without a significant impact on cognitive restraint (41, 46) or food aversions (47). Importantly, other energetics studies have revealed that altered energy intake rather than energy expenditure is the predominant driver of the negative energy balance induced by RYGBP (48, 49).

Mechanisms underlying effects of RYGBP

An accumulating body of evidence suggests that altered GI biology underlies the beneficial effects of RYGBP (Figure 2), which is now described as a metabolic rather than restrictive or malabsorptive procedure (28, 50). We now know that RYGBP results in rapid emptying of the gastric remnant (51), meaning any potential restrictive effect is largely negated. Malabsorption contributes only a small proportion to the reduction in net energy absorption due to RYGBP (52). Furthermore, nutrient stimulation of enteroendocrine chemosensory cells is enhanced (53), with resultant postprandial increases in gut hormone secretion (50), and the blunted postprandial circulating bile acid response associated with obesity is normalized (54, 55). These phenomena cannot be explained by mere restriction or malabsorption, and are now considered foremost among the effector mechanisms that underlie the metabolic benefits of RYGBP (50).

The gut hormone system has been extensively investigated in relation to the physiological changes induced by RYGBP (56). In particular, there is now a well-established body of research documenting markedly increased meal-stimulated peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) levels after RYGBP (57–66). The enhanced gut hormone responses occur as early as one or two days after RYGBP independent of weight loss per se (67), thus implicating a process directly related to the procedure itself. The enhanced responses are evident even with caloric intake as small as 75 kcal, demonstrate a dose-dependent increment (68), and remain persistently elevated in the long-term postoperatively (69). In general, these altered PYY and GLP-1 responses are associated with reduced hunger and increased satiety (66).

This altered hormonal milieu is highly relevant in the context of the known physiological roles of these gut hormones. Both PYY and GLP-1 act upon brain homeostatic and reward circuits to modulate feeding behavior (70–73); thus, enhancement of their secretion is a plausible mechanism for the effects of RYGBP on energy intake. Robust evidence from experimental imaging and translational studies indicate that the biologically active form of PYY, PYY3–36, mediates its anorectic effects predominantly by acting upon central appetite-regulating circuits, the hypothalamic arcuate nucleus and brain regions involved in food reward having been identified as key areas (73). In addition, there is strong evidence that circulating GLP-1 also has appetite-suppressing effects through direct activation of these centers in the brain, in a manner that is additive to PYY effects (72).

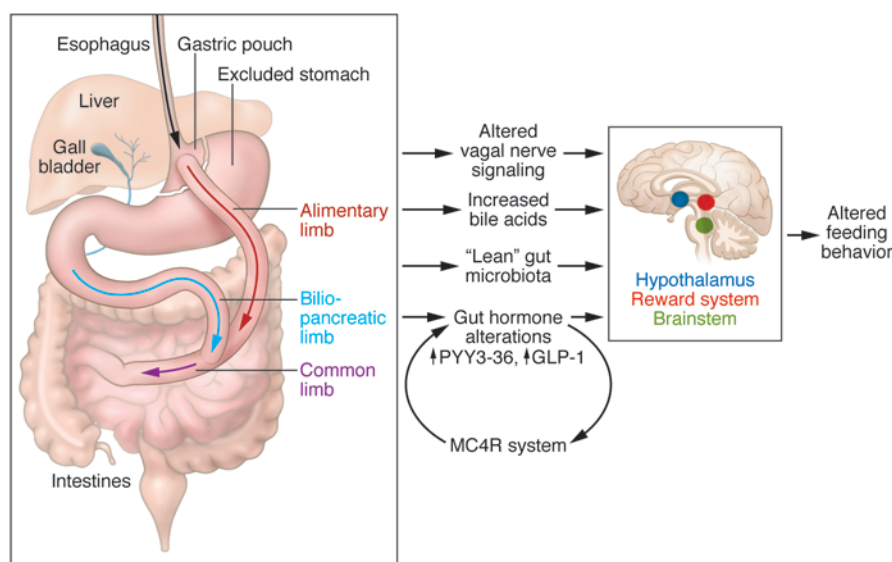


Figure 2. Schematic diagram illustrating the anatomy of RYGBP and the mechanisms leading to altered food intake. In RYGBP, nutrients rapidly pass through the small gastric pouch, bypassing the majority of the stomach and upper small bowel and directly entering the mid-jejunum. Nutrients meet pancreatic enzymes and bile acids at the common channel only. The anatomic modifications of RYGBP result in a higher secretion of PYY and GLP-1, and these hormonal changes are considered among the main mechanisms responsible for the altered food intake observed in RYGBP patients. Other proposed mechanisms include changes in gut microbiota, altered secretion of bile acids, and altered vagal nerve signaling. Since neural circuits ultimately determine feeding behavior, central effects on brain energy homeostatic centers are likely a final common pathway for each of these RYGBP effector mechanisms. MC4R, expressed on the basolateral membrane of L cells, may have an important role in augmenting RYGBP effects on PYY and GLP-1 secretion.

An array of human mechanistic and animal studies strongly suggests that the enhanced PYY and GLP-1 responses contribute to the anorectic effects of RYGBP. In two observational studies that stratified RYGBP patients according to weight loss response, the mean GLP-1 response was approximately 50% higher in the “good responders” than in the “poor responders,” with proportionate relative reductions in appetite (67, 74). Furthermore, inhibition of gut hormone responses, including the PYY response with the somatostatin analog octreotide in patients who had undergone RYGBP, results in increased hunger and increased food intake (60). In a rat model of RYGBP, blockade of endogenous PYY resulted in increased food intake (75). Additionally administration of the GLP-1R antagonist exendin(9-39) increased food intake but did not alter energy expenditure after RYGBP (76). Other investigators found that GLP-1R inactivation did not affect food intake and body weight changes post-RYGBP (77, 78); however, such studies utilizing models of functional GLP-1R inactivation should be interpreted with caution in terms of effects on body weight and energy balance, due to the potential confounding effects of lower body weight in GLP-1R knockout mice (77, 78). Furthermore, global GLP-1R deletion and central GLP-1R antagonism not only abolish the effects of peripherally produced GLP-1 but also those of centrally produced GLP-1, which itself plays a role in regulating energy homeostasis (79, 80).

Animal studies using other models of bariatric surgery, including ileal transposition (IT) and enterogastroanastomosis (EGA), provide further evidence of the importance of the enhanced

post-RYGBP PYY and GLP-1 responses. Rats who had undergone IT exhibited reduced food intake and, importantly, increased PYY and GLP-1 expression within the transposed segment, coupled with increased circulating PYY and GLP-1 levels compared with controls who had intestinal transections and reanastomosis without transposition (81). A study employing EGA provided direct evidence that PYY plays a key mechanistic role in surgical weight loss (82). EGA in wild-type mice with diet-induced obesity (DIO) exhibited significantly more weight loss and higher PYY and GLP-1 levels compared with sham surgery; however, in obese *Pyy* knock-out mice, weight loss was equivalent after EGA and sham surgery (82), suggesting that PYY is necessary for postoperative weight loss and is presumably driven by reductions in food intake.

Other gut hormones known to modulate feeding behavior, such as the orexigenic hormone ghrelin (70) and anorexigenic hormones cholecystokinin (CCK) and oxyntomodulin (83), have also been studied in the context of RYGBP. The potential role that altered ghrelin secretion plays after RYGBP was first highlighted in the landmark study by Cummings et al., which showed markedly suppressed 24-hour

secretory profiles of total ghrelin in RYGBP patients 9–31 months after the procedure (84). This finding was in contrast to the profile of increased total ghrelin secretion, which was observed after dieting (84). Indeed, one might anticipate reduced postprandial suppression of ghrelin secretion (higher ghrelin secretion) in the post-RYGBP state, since ghrelin-secreting cells in the gastric fundus and duodenum are excluded from nutrient contact albeit while remaining in situ (Figure 2). In addition, the suppression of active ghrelin (acyl-ghrelin) levels was found to be more pronounced than that of total ghrelin levels approximately three years after RYGBP (57), although there is conflicting evidence in this regard (85). While further studies have demonstrated a fall in ghrelin secretion in the short term following RYGBP (65, 66, 86), the overriding consensus points to a return of ghrelin secretion to preoperative levels in the long term (e.g., one year) (86–88). Regardless of these discrepancies, studies in good and poor responders (60, 74) suggest that any changes in ghrelin secretion are not sufficient to affect weight outcomes following RYGBP, although both of these studies measured total ghrelin and not acyl-ghrelin. Nevertheless, that ghrelin secretion is not markedly altered in the context of sustained caloric restriction following RYGBP is notable in itself. Studies that address the effects of RYGBP on changes in, for example, PYY and acyl-ghrelin hormone ratios, instead of isolated gut hormone levels, may establish a clearer relationship between the anorectic effects of RYGBP and those of gut hormones. Secretion of oxyntomodulin, like its L cell co-secreted counterparts GLP-1 and PYY, is enhanced in both the short term (one month) (89)

and the long term (measured indirectly at three years) (86) postoperatively. Interestingly, the anorectic effects of oxyntomodulin are additive to those of PYY in obese humans (90), indicating a biologically plausible role for this L cell product in mediating the effects of RYGBP on feeding behavior. In contrast, CCK levels are not significantly altered after RYGBP (74, 88).

Alternative candidate mechanisms (Figure 2) that might have a role in inducing the anorectic response and weight loss produced by RYGBP include changes in the secretion of bile acids (54) and the ileal-derived, bile acid-stimulated enterokine FGF-19 (91), a shift toward a “lean” gut microbiota phenotype (92), or altered vagal nerve signaling (93). Indeed, altered bile acid signaling through the farnesoid-X receptor (FXR) is thought to be a critical factor in mediating the effects of an alternative metabolic procedure, sleeve gastrectomy (SG), on food intake and weight loss (94). However, there is markedly contrasting functional anatomy between RYGBP and SG, with expedited proximal mixing of nutrients with bile acids in SG and delayed mixing at the common channel in RYGBP (Figure 2). Bile acid dynamics are thus likely to differ between procedures; indeed, differences in postprandial elevations of circulating bile acids at one year (higher in RYGBP) have been reported (95), although it is unclear whether FXR signaling is critical in RYGBP. Understanding the tridirectional interplay between altered microbiota, bile flow, and hormonal responses in the post-surgery intestinal milieu is increasingly viewed as key to unraveling the metabolic benefits of RYGBP (96); however, at present, mechanistic roles of altered bile acids or gut microbiota in feeding behavior changes induced by RYGBP are far less well established than the roles of gut hormones. In fact, alterations in bile flow are more likely to affect energy expenditure than energy intake (97), and transmission of gut microbiota from RYGBP mice to germ-free mice to germ-free mice resulted in weight loss but no effect on food intake (92). Because neural circuits ultimately determine feeding behavior, central effects on brain energy homeostatic centers are likely to be a final common pathway for each of these RYGBP effector mechanisms (Figure 2). In this regard, there has been an increasing interest in the role that altered hedonic feeding may play in mediating the effects of RYGBP on energy intake (29, 98).

Insights from neuroimaging

Recent neuroimaging studies have also started to shed light upon the changes in hedonic drive observed following RYGBP (Table 1). Although these studies are quite diverse in terms of experimental protocols, impeding direct comparison of the outcomes, a number of interesting findings relating to RYGBP effects on hedonic feeding behavior are apparent. First, there are differences in activation of brain reward centers in response to food cues in patients before and after RYGBP. Using fMRI brain scanning, Ochner and colleagues demonstrated that high- but not low-palatability food cues produced less mesolimbic reward pathway activation 1 month after RYGBP compared with before RYGBP (99). In a separate study, the same group showed that postoperative reductions in mesolimbic responsivity were associated with postoperative reductions in “wanting” (anticipatory reward) but not “liking” (consummatory reward) (100). In yet another study by Ochner and colleagues, the previously observed postopera-

tive changes in neural responsivity were replicated in the fasted but not the fed state (101). At first glance, this finding appears to contradict expected fed-fasted differences in neural responsivity to food cues following RYGBP, given the enhanced postprandial secretion of PYY and GLP-1. However, while it is clear that PYY in particular modulates neuronal activity acutely at circulating levels equivalent to the postprandial state (73), the effects on neural responsivity of repetitive exaggerated increases in PYY secretion as seen following RYGBP are not known. Second, weight loss alone is unlikely to account for these changes in reward center activation. Scholtz et al. reported that RYGBP patients exhibited markedly reduced brain reward system activation in response to viewing high-calorie food images compared with BMI-matched gastric band patients, despite similar weight loss (102). Third, reduced brain reward center activation appears to be associated with a shift in food preference away from high-caloric-density foods (99, 102). Fourth, changes in reward center activation following RYGBP are likely to be independent of striatal D2/3R availability (103). Finally, neural responsivity to food images in the long term (more than three years) in women who had undergone RYGBP resembled that of lean individuals, despite still remaining above normal weight (104). In addition, long-term postoperative neural responsivity was in marked contrast to that observed in nonoperated obese individuals, who exhibited higher activation of reward-related areas such as the anterior cingulate cortex and orbitofrontal cortex (104).

Insights from animal models

An accumulating body of research in animal models corroborates many of the feeding behavior changes observed following RYGBP (105). However, these animal studies should be interpreted with caution due to important differences in the rodent stomach and rodent feeding behavior (106, 107), both of which could adversely affect interpretation of RYGBP-induced outcomes. Furthermore, changes in rodent feeding following bariatric surgery are often not prolonged (108); thus, delineation of the relevant biological processes is challenging. Nevertheless, an obvious advantage of studies in animal models of RYGBP is that the confounding factor of pre- and postoperative dietary advice and counseling, typically provided to human bariatric surgical patients, is removed from the equation. A shift in preference away from fat toward lower-caloric-density foods has been consistently demonstrated in studies comparing RYGBP rats with sham-operated rats (107–111). Of note, while these studies all employed obese rodents fed high-fat diets, rodent studies that found no apparent reduction in food intake used normal-weight animals that were fed regular chow (112, 113), emphasizing the model dependence of these RYGBP studies. This shift to low-palatability foods has also been found to associate with reduced wanting in an incentive runway task and less liking (vigorous licking) in brief access tests of palatable rewards (109). Thus, these studies have provided an additional layer of evidence implicating altered hedonic feeding in mediating the changes in feeding behavior observed after RYGBP. Notably, rodent studies investigating the role of vagal innervation in RYGBP-induced hypophagia generally support the notion that vagal neural signaling contributes to the effects of RYGBP on food intake (114, 115), albeit with a differential time course of the effect between these studies. Vagal sparing during RYGBP resulted in

Table 1. Summary of neuroimaging studies undertaken in RYGBP patients

Reference	Imaging	Subjects (N, F/M)	Timing after operation	Comparison	Intervention	Feeding protocol	Outcome(s)	Interpretation
Ochner et al. (99)	fMRI with visual and auditory food representation	10 RYGBP (10 F/0 M)	4 wk	Before and after RYGBP	VAS (hunger and satiety)	Liquid meal 250 ml, 250 kcal, 60 min before fMRI	Post-RYGBP reductions in brain activation within areas involved in reward processing together with reduced desire to eat; findings were greatest in response to food cues of high versus low caloric density	RYGB surgery alters the neural responses to environmental food cues, with less anticipatory brain activation elicited when subjects are exposed to high-calorie foods in particular; these changes may underlie changes in feeding behavior after surgery
Ochner et al. (100)	fMRI with visual and auditory food representation	14 RYGBP (14 F/0 M)	4 wk	Before and after RYGBP	VAS (wanting and liking)	Liquid meal 250 ml, 250 kcal or water 250 ml, 60 min before fMRI	Post-RYGBP reductions in mesolimbic neural responsivity, together with reduced wanting of high- versus low-calorie food cues; decreases in relative neural responsivity (high- versus low-calorie food cues) predicted reductions in wanting of high- versus low-calorie foods	Greater relative reductions in reward-related activation (wanting and liking) were found for high- versus low-calorie food cues post-RYGBP, which suggests a preferential reduction in expected reward value of high- versus low-calorie foods
Ochner et al. (101)	fMRI with visual and auditory food representation	5 RYGBP (5 F/0 M)	4 wk	Before and after RYGBP (fasted and fed states)	VAS (hunger and satiety)	Liquid meal 250 ml, 250 kcal or water 250 ml, 45 min before fMRI	Post-RYGBP decreases in insula, ventromedial prefrontal cortex, and dorsolateral prefrontal cortex responsivity in fasted but not fed state	Contrary to the authors' predictions, there were greater reductions in neural responsivity in the fasted state relative to the fed state, and the difference was greater before RYGBP than after RYGBP
Scholtz et al. (102)	fMRI with food pictures	21 RYGBP (17 F/4 M)	>8 wk	20 AGB (19 F/1 M), 20 obese (17 F/3 M)	VAS (appetite and food palatability) and blood samples (including measurement of PYY, GLP-1, acyl-ghrelin, and bile acids)	Ad libitum ice cream test meal after fMRI	RYGBP patients had lower activation than AGB patients in brain reward areas, particularly with high-calorie foods, associated with lower palatability and appeal of high-calorie foods in RYGBP patients compared with AGB patients and/or BMI-matched, nonoperated controls; GLP-1, PYY, and bile acids were increased in RYGBP patients	Obese patients have lower brain hedonic responses to food after RYGBP surgery compared with gastric banding
Frank et al. (104)	fMRI with food pictures	9 RYGBP (9 F/0 M)	3.4 ± 0.8 yr	11 obese (11 F/0 M), 11 normal weight (11 F/0 M)	VAS (for hunger/satiety), Three-Factor Eating Questionnaire	Liquid meal 300 ml, 246 kcal, 30 min before fMRI	Obese women showed altered brain activation to food images compared with normal-weight women; no differences in brain activity were observed between normal-weight and RYGBP groups; RYGBP group rated lower on hunger and higher on satiety than obese and lean groups	RYGBP reverses the altered brain activity pattern observed in severely obese women
de Weijer et al. (103)	MRI + SPECT	19 RYGBP (19 F/0 M)	6 wk	Before and after RYGBP	Hyperinsulinemic-euglycemic clamp with a stable glucose isotope tracer	None	No significant change in D2/3R availability before versus 6 weeks after RYGBP	RYGBP does not significantly alter striatal D2/3R availability in morbidly obese women

AGB, adjustable gastric banding; F, female; M, male; SPECT, spectroscopy; VAS, visual analog scale. Enteroendocrine MC4R augmentation of PYY/GLP-1 secretion could result in increased production of MC4R ligand centrally, which if transferred to the systemic circulation could theoretically act on enteroendocrine MC4R, thus representing a feed-forward mechanism in the control of energy intake.

lower food intake compared with rats in which the vagal nerve was not preserved, either through complete paraesophageal neurovascular bundle ligation (114) or celiac branch vagotomy (115), but not with hepatic branch vagotomy (116). The inconsistent findings among vagotomy studies may reflect methodological differences, for example in the specific vagal lesioning employed, in the diets used (regular chow [ref. 114], high-fat [ref. 115], or three-choice diet [ref. 116]), or in the preoperative weight status of the rodents (weight-gaining [ref. 114, 115] or weight-stable [ref. 116]). Although the role of vagal

signaling in the effects of RYGBP on humans remains unclear (117), evidence from subjects with truncal vagotomy who had not undergone RYGBP suggests that intact vagal innervation may be important for the anorectic actions of GLP-1, one of the key candidate effectors of RYGBP-induced hypophagia (118).

Role of the MC4R pathway

Given the role of the central MC4R system in the control of energy balance (5) and pathophysiology of human obesity (119),

it is not surprising that the model of MC4R perturbation has been employed to interrogate the biological pathways underlying RYGBP effects. Severely obese individuals with heterozygous mutations of *MC4R* benefit from RYGBP to a similar extent as individuals without *MC4R* mutations (120, 121), suggesting that one functional copy of *MC4R* is sufficient to permit RYGBP effects on energy intake. However, rodent studies suggest that MC4R function is critical for the sustained reductions in food intake and weight loss engendered by RYGBP, as demonstrated by studies undertaken in *Mc4r*-null mice (120). These studies suggest either that non-MC4R-mediated mechanisms by which RYGBP affects energy balance are not powerful enough to overcome complete absence of MC4R signaling or that the MC4R system is intrinsic to the biological response to RYGBP (Figure 2). Importantly, carriers of a *MC4R* variant (I251L), known to increase basal MC4R activity, experience significantly greater weight loss after RYGBP compared with noncarriers or carriers of other *MC4R* variants (122).

Understanding the role of MC4R in mediating the biological response to RYGBP could yield important insights into how RYGBP results in resetting the body weight set-point (29). Interestingly, a study employing intracerebroventricular administration of a specific MC4R antagonist in RYGBP and sham-operated rats demonstrated that while central MC4R blockade led to doubling of food intake and weight regain, the reduction in meal size produced by RYGBP was unaffected (123). Restoration of MC4R in key preganglionic autonomic motor neurons of *Mc4r*-null mice demonstrated that MC4R expression in these neurons was important for RYGBP-induced reductions in food intake, but the effect was greater for RYGBP effects on energy expenditure (124). While these studies highlight the critical role of the melanocortin pathway in regulation of energy intake, they establish that central melanocortin signaling is not the critical mechanism responsible for the anorectic effects of RYGBP, in particular, the RYGBP-induced reduction in meal size, which is clearly central to the feeding changes observed in humans after RYGBP (41).

Of key relevance to the effects of RYGBP on meal size is a recent study that provided convincing evidence for a direct physiological role of MC4R expressed on enteroendocrine L cells in regulating secretion of PYY and GLP-1 (125). The study described an enteroendocrine MC4R system that acts as a positive regulator of PYY and GLP-1 release in vivo (125). Thus, MC4R expressed on the L cells could augment RYGBP effects on PYY and GLP-1 secretion. Indeed, L cell MC4R-driven PYY/GLP-1 enhancement could explain why carriers of *MC4R* variant (I251L), which is known to increase basal MC4R activity (126), experience greater weight loss after RYGBP compared with noncarriers or carriers of other

MC4R variants (Figure 2 and ref. 122). Enhanced coupling of this L cell MC4R pathway with central melanocortin signaling in RYGBP offers a potential explanation for RYGBP-induced resetting of the energy balance set-point. The peripheral MC4R augmentation of PYY/GLP-1 secretion could result in increased production of MC4R ligand centrally, which if transferred to the systemic circulation could theoretically act on enteroendocrine MC4R, thus representing a feed-forward mechanism in the control of energy intake (Figure 2).

Conclusions and future perspectives

Elucidation of the mechanisms governing alterations in feeding behavior induced by RYGBP is critical to our understanding of why RYGBP has been so successful for the millions of patients who have undergone the procedure since the 1980s. The actions of PYY and GLP-1 on brain energy homeostatic centers are well established, and the effects of RYGBP on these gut hormones are well documented. Taken together with the emerging importance of an enteroendocrine MC4R pathway, there is mounting evidence for a place of L cell responses at the center of the biological model of RYGBP effects on feeding behavior. Though they wield huge potential, neuroimaging studies have yet to make a serious impact on bariatric surgery research, or on obesity research in general. Future studies may incorporate simultaneously assessed neural responsivity and circulating gut hormones in the meal-stimulated post-RYGBP setting. Additionally, gender-specific mechanistic studies involving genotype-stratified and obesity phenotype-matched subjects would greatly enhance this field of research. Studies comparing RYGBP with SG, another metabolic procedure with differential biological effects from those of RYGBP (66, 88, 105, 127, 128), might also yield important insights into the mechanisms underlying the changes in food preference, hedonic feeding, and neural responsivity. Future research might also employ these bariatric procedures, using a Mendelian randomization experimental approach, as a tool to probe the physiological and genetic mechanisms underlying obesity.

Acknowledgments

S. Manning was funded by the Rosetrees Trust and the National Institute of Health Research University College London Hospitals Biomedical Research Centre. A. Pucci is supported by the Rosetrees Trust.

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