



# The neurohormonal regulation of energy intake in relation to bariatric surgery for obesity

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## ABSTRACT

Obesity has reached pandemic proportions, with bariatric surgery representing the only currently available treatment demonstrating long-term effectiveness. Over 200,000 bariatric procedures are performed each year in the US alone. Given the reliable and singular success of bariatric procedures, increased attention is being paid to identifying the accompanying neurohormonal changes that may contribute to the resulting decrease in energy intake. Numerous investigations of postsurgical changes in gut peptides have been conducted, suggesting greater alterations in endocrine function in combination restrictive and malabsorptive procedures (e.g., Roux-en-Y gastric bypass) as compared to purely restrictive procedures (e.g., gastric banding), which may contribute to the increased effectiveness of combination procedures. However, very few studies have been performed and relatively little is known about changes in neural activation that may result from bariatric procedures, which likely interact with changes in gut peptides to influence postsurgical caloric intake. This review provides a background in the neurohormonal regulation of energy intake and discusses how differing forms of bariatric surgery may affect the neurohormonal network, with emphasis on Roux-en-Y gastric bypass, the most commonly performed procedure worldwide.

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Currently, bariatric surgery represents the only form of treatment for obesity that demonstrates long-term effectiveness [1–3]. From 1992 to 2006, a ten-fold increase in obesity surgeries was observed [4]. The most common forms of bariatric surgery are Roux-en-Y gastric bypass (RYGB) and adjustable gastric banding (AGB), which together account for approximately 90% of the procedures performed today [5]. Postsurgical reductions in body weight result largely from the restrictive and/or malabsorptive effects of the bariatric procedures. However, these mechanisms alone appear to be insufficient to account for the reductions in caloric intake and body weight seen postsurgically [6–8], even in purely restrictive procedures such as AGB [7,9]. Alterations in the neurohormonal regulation of energy intake have been proposed to contribute to postsurgical reductions in caloric intake, particularly in RYGB [8,10–12].

## 1. Hormonal influences on energy intake regulation relevant to bariatric surgery

Numerous hormones are involved in controlling appetite and food intake via the activation of brain areas, primarily within the limbic and mesolimbic systems [13]. Hunger and satiety signals from adipose tissue (leptin), the pancreas (insulin) and the gastrointestinal tract (cholecystokinin [CCK], glucagon-like peptide-I [GLP-1], peptide YY<sub>3–36</sub> [PYY<sub>3–36</sub>]) are involved in relaying information about energy status through the neurohormonal gut–brain axis primarily targeting the hypothalamus and brainstem [13]. The major appetite-related peptides, which act through the central nervous system (CNS) to help regulate energy balance and may be affected by bariatric surgery, are introduced below.

### 1.1. Ghrelin

Secreted mainly by the stomach, ghrelin is an orexigenic peptide that acts on hypothalamic neurons through the bloodstream via vagal afferents containing ghrelin receptors, as well as through direct release within the hypothalamus [14]. In animals, central ghrelin

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administration also enhances the secretion of the orexigenic neuropeptides neuropeptide-Y (NPY) and agouti-related peptide (AgRP) in the arcuate nucleus (AN) of the hypothalamus [15]. Ghrelin has also been shown to activate dopamine neurons in the ventral tegmental area (VTA) and promote dopamine turnover in the nucleus accumbens (NA) of the ventral striatum [16]. This effect on reward processing in the mesolimbic dopaminergic pathway may be an integral part of ghrelin's orexigenic action [17,18], supported by evidence that blocking ghrelin receptors in the VTA decreases food intake [16].

### 1.2. Peptide YY (PYY)

PYY is an anorexigenic lower gut-derived hormone synthesized from L entero-endocrine cells [19]. PYY mediates its actions via Y1–Y5 receptors [19], and the binding of the active component of PYY<sub>3–36</sub> to Y2 receptors on vagal afferents leads to activation of the arcuate nucleus to suppress NPY activation [20]. Delayed gastric emptying (via the ileal brake mechanism) also contributes to the inhibitory effect of PYY<sub>3–36</sub> on appetite and food intake [21].

### 1.3. Glucagon-like peptide 1 (GLP-1)

Co-released with PYY, GLP-1 is an anorexigenic peptide that is secreted postprandially from the distal gastrointestinal tract. GLP-1 acts as an ileal brake for the upper GI tract and decreases food intake in part by inhibiting gastric emptying, resulting in greater gastric distension [22]. Endogenous GLP-1 affects hypothalamic signaling through vagal afferent neurotransmission [23,24] and by entering the peripheral circulation. Circulating levels of GLP-1 are higher prior to and following food consumption in lean as compared to obese individuals [25].

### 1.4. Cholecystokinin

An endogenous hormone present in the GI tract and the brain, cholecystokinin (CCK) helps control meal size and duration via a feedback signaling network involving the periphery and the CNS [26]. CCK reaches peak levels within 15–30 min [27,28]. CCK activates receptors on the vagus nerve, which transmit satiety signals to the dorsomedial hypothalamus and minimizes NPY action [27].

### 1.5. Leptin

An anorexigenic hormone synthesized from adipose tissue, leptin helps control adipose metabolism by stimulation of lipolysis and suppression of lipogenesis [29]. It crosses the blood brain barrier and transmits signals about metabolic status from the periphery to hypothalamic regulatory centers [30]. Once bound to its central receptor, leptin down-regulates appetite stimulating neuropeptides (e.g., NPY, AgRP) while up-regulating anorexigenic alpha-Melanocyte-stimulating hormone, cocaine-and amphetamine-regulated transcript and corticotropin-releasing hormone [30]. Leptin injections in obese humans have not been efficacious in reducing food intake and weight gain, potentially due to the development of leptin resistance [31]. Studies also suggest that leptin can influence the reward value of food [32,33] and leptin administration can help maintain lost weight [34].

### 1.6. Insulin

Secreted from the pancreas, insulin varies directly with adiposity, and visceral fat is negatively correlated with insulin sensitivity [35]. Basal and postprandial insulin are greater in obese than in lean individuals [36]. Insulin can penetrate the blood brain barrier

and binds to receptors in the AN to decrease food intake [37]. See Table 1 for a brief summary of the major appetite-related peptides relevant to bariatric surgery and their proposed effects on hunger or satiety.

## 2. Neuroimaging and energy intake regulation in relation to bariatric surgery

Neuroimaging is increasingly becoming more common in obesity research as investigators attempt to understand the biological basis of eating behavior. Positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) are common neuroimaging techniques used to assess brain activity and provide insight into brain systems linked to feeding behavior (See [38] and [39] for reviews).

The neural systems involved in energy intake regulation are complex but can be roughly divided into two related systems, the homeostatic and hedonic networks [12,17]. The homeostatic system is comprised of the hypothalamus and brainstem, driven mainly by hypothalamic activity [12,17]. The hypothalamus, especially the arcuate nucleus, integrates peripheral hormonal signals and receives inputs from the brainstem, which detects vagal signals related to ingestion [40]. It is responsible for the assimilation of input about internal hunger and satiety signals and the propagation of appropriate output signals to other relevant brain areas (e.g., upward moderation of mesolimbic reward areas to increase the reward salience of food during caloric deprivation) [13,41]. Thus, the homeostatic system drives food intake based on caloric need in order to maintain energy balance and body weight [17,42], which may be determined by a biological settling point [43].

In contrast, the hedonic system drives food intake based on the perceived reward value of food [17,44], operating largely through dopaminergic signaling in the mesolimbic pathway [45]. The mesolimbic pathway initiates behavioral responses based on the predicted reward, or hedonic, value of stimuli encountered in the environment [12,44]. Major components of this complex neural system include the amygdala, hippocampus, VTA, and striatum (caudate, NA, and lentiform nucleus), and these areas have strong functional connections to areas within the prefrontal cortex (PFC; e.g., dorsolateral PFC, orbitofrontal cortex [OFC]) [45]. The PFC is responsible for integrating internal and external sensory information, reward-related information from other cortico-limbic areas and signals from the hypothalamus, which can modulate reward salience [13,17]. The PFC is also connected to other cortical areas involved in motor planning and execution [46].

The relatively limited number of studies that have examined brain activation in relation to food intake or body weight are mainly cross-sectional and focus on the differences in reaction to food stimuli between types of stimuli (e.g., high vs. low-palatability) or body mass index (BMI; e.g., lean vs. obese) [47,48]. The majority of studies in this area coalesce in reporting greater activation in hedonic system activation in response to high- vs. low-palatability stimuli and in obese vs. lean

**Table 1**

Major appetite-related peptides relevant to bariatric surgery.

Gut peptides	Central effects on appetite	Alterations due to RYGB <sup>a</sup>
Ghrelin	↑	↓
PYY	↓	↑
GLP	↓	↑
CCK	↓	→
Leptin	↔	↓
Insulin	↔	↓

↑ = increase. ↓ = decrease. → = no significant change.

↔ = modifies effect depending on energy balance.

<sup>a</sup>According to the majority of study findings to date.

individuals [49,50]. Such findings potentially reflect greater perceived hedonic reward of high (vs. low) palatability food cues and heightened sensitivity to reward in obese (vs. lean) individuals [51,52].

As noted, reward value is largely processed in the PFC, which receives visual, auditory, and orosensory inputs from the thalamus, as well as information from the hypothalamus [12]. There is evidence to suggest that the hypothalamus may modulate reward salience [53–55], which may explain why individuals in a state of caloric need (fasted) show increased sensitivity to, and preference for, sweet and novel tastes [56,57], as well as greater activation of hedonic network brain areas in response to appetitive stimuli [54,58,59]. Conversely, in a fed state (in the presence of postprandial satiety signals), individuals show decreased hedonic network activation in response to appetitive stimuli [54,59]. However, the hedonic system can override attempts by the homeostatic system to maintain energy balance, and drive food intake even in the presence of postprandial satiety signaling [60,61]. Variation in the ease with which satiety signals are overridden by the perceived reward value of food may reflect individual differences in appetitive responsivity, or the desire to eat following exposure to food cues [49].

### 3. Interactions between gut peptides and brain systems relevant to bariatric surgery

Neurological and hormonal systems are often studied independently, but hunger and satiety signals are mediated by a complex interplay of both systems, the neurohormonal pathway [62]. Ghrelin, PYY, GLP-1, CCK, insulin and leptin are primarily released in the periphery in response to the presence or absence of nutrients in the digestive tract [63,64] but act indirectly on the vagus nerve and/or directly on target areas of the hypothalamus [65], propagating potent hunger and satiety signals to the brain. In addition, gut peptide signaling may have more complex neurobehavioral actions in triggering hypothalamic modulation of the perceived reward value of food via the mesolimbic pathway [66]. See Fig. 1.

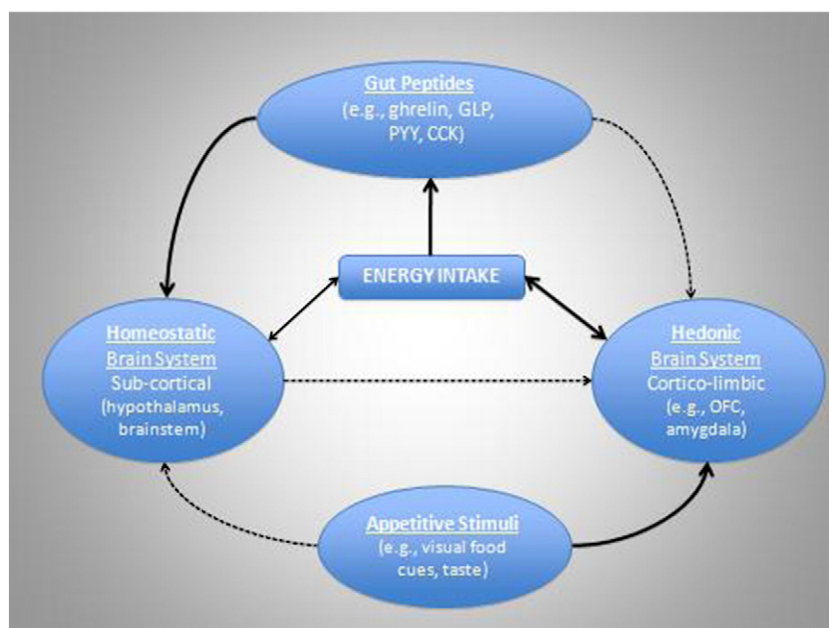
#### 3.1. Neuroimaging and appetite-related hormones

A novel technique for examining *in vivo* gut–brain interactions in humans is to combine neuroimaging with gut hormone measures or manipulations. Farooqi et al. [67] used fMRI to show that heightened

activation in the ventral striatum in response to food cues in two leptin-deficient adolescents was significantly reduced following one week of leptin administration. In other fMRI studies, Rosenbaum et al. [68] showed that a number of changes in brain activation typically associated with increased hunger, which resulted from non-surgical weight loss, were leptin-reversible. Similarly, Baicy et al. [69] reported reduced brain activity in regions linked to hunger (insula, parietal and temporal cortex) in genetically leptin-deficient adults following leptin replacement. These studies are consistent with evidence suggesting that leptin may suppress appetite by down-regulating brain areas associated with drive to eat while up-regulating areas associated with homeostatic control and satiety [33,67].

In an fMRI study of ghrelin infusion, Malik et al. [17] found post-infusion increases in activation in the amygdala, OFC, insula and striatum in response to pictures of highly palatable food in lean males given a 20 min ghrelin infusion, suggesting that some portion of ghrelin's orexigenic effects may come through the enhancement of the perceived reward value of food. Animal studies [18,70] further implicate an interaction between ghrelin and mesolimbic pathway activation in showing that ghrelin can activate dopamine neurons in the VTA and increase dopamine in the nucleus accumbens, which may stimulate food intake [15,16].

In a study of food-induced hormonal changes, Pannaciuoli et al. [71] measured GLP-1 levels and PET activation before and after administered a satiating amount of a liquid formula meal to lean adult subjects. Postprandial increases in GLP-1 were found to correlate positively with increases in activity in the dlPFC and hypothalamus, suggesting that GLP-1 may mediate the purported role of the dlPFC in the cessation of eating (satiety signaling) [71,72]. Finally, in an innovative study of real-time interactions between changes in gut hormone levels and brain activation, Batterham et al. [73] infused PYY<sub>3–36</sub> at a rate designed to mimic that which would be expected in response to a meal and assessed brain activation concurrently, using fMRI. These authors showed that increases in PYY<sub>3–36</sub> were associated with increased activity in the OFC, parabrachial nucleus, midbrain VTA, insula, anterior cingulate, ventral striatum and posterior hypothalamus. They also reported a PYY<sub>3–36</sub>-induced shift from homeostatic (hypothalamic) to hedonic (OFC) brain areas in predicting subsequent food intake, which may reflect a switch from homeostatic to hedonic control of appetite with the introduction of a postprandial satiety signal.



**Fig. 1.** Cartoon representation of the relevant influences on energy intake. The strength of evidence in support of each association is represented by the thickness of the connecting arrows with bolded lines representing strong empirical support and the dotted lines representing more theoretical evidence.

#### 4. Surgical interventions for obesity

Surgical interventions are not only more effective than behavioral treatments in the short term but are the only form of obesity intervention with evidence of consistent long-term effectiveness [1,3]. Current surgical interventions for obesity all contain a restrictive component, limiting the amount of food that can enter the stomach pouch as well as the rate at which food can be ingested. Several procedures, most notably RYGB, also contain a malabsorptive part in which the bowel length is shortened, decreasing nutrient and calorie absorption. However, there is controversy regarding the degree and durability of postsurgical malabsorption associated with these procedures [74]. The purely restrictive AGB procedure is gaining popularity, currently representing approximately 25% of procedures [1,75], second only to RYGB, which accounts for approximately 65% of procedures worldwide [1]. Gastric bypass results in more weight loss than gastric banding (GB). The Swedish Obese Subjects [76] study showed that the maximal percent of initial weight lost (1–2 yr post-surgery) was  $32\pm 8$  SD in RYGB vs.  $20\pm 10$  in GB and this difference was maintained at 10 yr follow up (25% in RYGB vs. 14% in GB). Similarly, at 2-yr follow up, Shah et al. [77] reported reductions of approximately 31% of initial body weight in RYGB vs. 24% in GB. Descriptions of these and other procedures are provided below.

Most purely restrictive procedures create a small gastric pouch with a narrow outlet, limiting the intake of food without disruption of the absorptive function of the small intestine. With VBG, a longitudinal staple line with a tight outlet wrapped by a band or mesh partitions the cardia (proximal part) from the rest of the stomach (Fig. 2A), whereas AGB involves encircling the upper part of the stomach (distal to the gastroesophageal junction) with a tight, adjustable, prosthetic band (Fig. 2B). The amount of restriction in AGB may be altered by the addition or withdrawal of saline solution from the hollow core of the band [78]. Sleeve gastrectomy, intragastric balloon, and endoluminal gastropasty are other forms of restrictive procedures that are less commonly used. Conventional malabsorptive bariatric operations predominantly circumvent a portion of the small intestine in an effort to reduce nutrient absorption. The jejunoileal bypass (JIB) is an example of a purely malabsorptive technique, which separates the jejunum near the ligament of Treitz and reconnects it near the ileocecal valve, bypassing a long small bowel segment (Fig. 3A). However, this procedure is rarely performed due to significant complications and relatively greater need for revision surgeries [78].

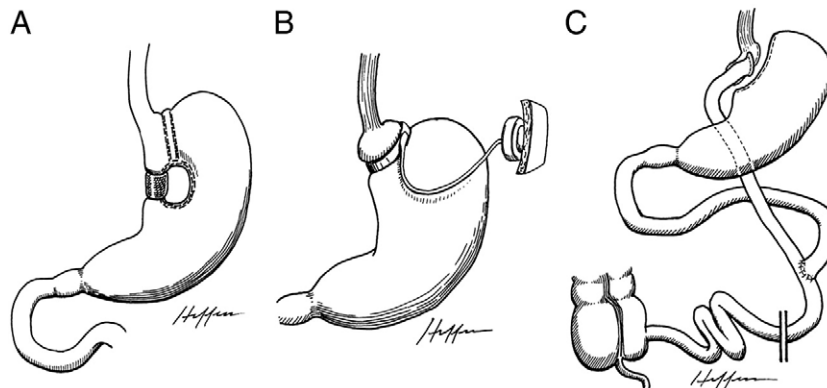
Combination bariatric procedures incorporate both restrictive and malabsorptive components. Biliopancreatic diversion (BPD) consists of a distal horizontal gastrectomy, where the remnant stomach is anastomosed to the distal small intestine (alimentary limb). The excluded small intestine carries the bile and pancreatic secretions, and is anastomosed to the short bowel channel proximal to the

ileoceleal valve, leaving a short common limb portion for the mixing of nutrients with secretions (Fig. 3B). The BPD is also limited in use due to adverse health outcomes related to essential nutrient malabsorption [79]. The biliopancreatic diversion with duodenal switch (BPD-DS) includes a sleeve vertical gastrectomy where the gastric fundus is mostly resected, with duodenal closure a few centimeters distal to an intact pylorus facilitating a duodeno-ileal anastomosis (Fig. 3C). This procedure is chiefly performed on super-obese patients ( $\text{BMIs} > 50 \text{ kg/m}^2$ ), as it classically leads to relatively large postsurgical weight loss; however, it is not commonly performed due to adverse health outcomes similar to those seen in BPD [78]. Lastly, RYGB surgery represents the most common bariatric procedure and is considerably more effective than AGB. With RYGB, a small gastric pouch is created and anastomosed to the jejunum with a short Roux-en-Y alimentary limb of distal small bowel, bypassing the majority of the stomach, the entire duodenum and a portion of the jejunum (Fig. 2C).

Despite a rapid increase in the number of studies on bariatric surgery, the precise mechanisms of action are still not well understood, particularly with RYGB [8,80]. While the restricted (15–50 mL) postsurgical pouch size limits ingestive capacity [8] and the bypassing of the upper portion of the small intestine may prevent a small percentage of ingested calories from being absorbed into the body [8,74], these mechanisms account for only a proportion of postsurgical weight loss [8,10,81]. Evidence for this comes from research demonstrating corrective adaptation to the malabsorptive component [74] and limited small meal adaptation [82], as well as subjective reports [83,84] and behavioral data [85,86] suggesting that presurgical preferences for foods high (vs. low) in fat [84], calories [85], and palatability [83,87] are reduced or eliminated following RYGB (but not AGB) surgery. Finally, preliminary data from our laboratory suggest that there may also be a greater reduction in non-specific (to any particular food) desire to eat in response to high-calorie, relative to low-calorie food cues following RYGB. The neurohormonal system has been repeatedly implicated in accounting for this unexplained reduction in postsurgical caloric intake [8,10–12]. Numerous investigations of appetite-related gut peptides have resulted and are described below.

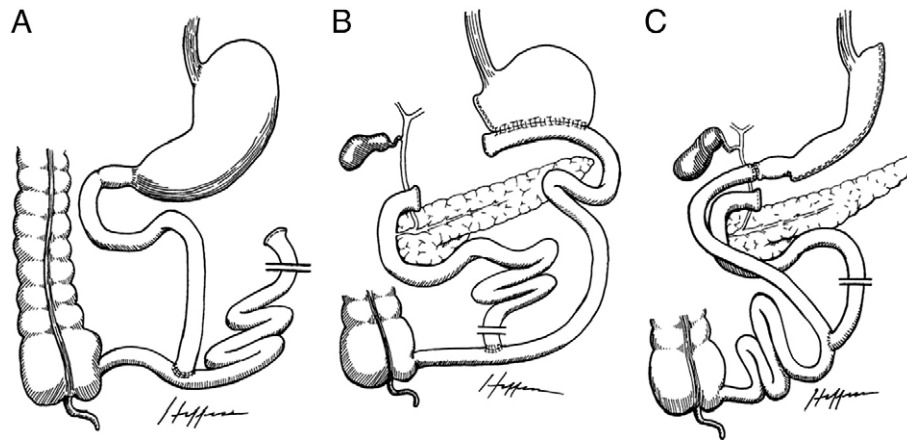
#### 5. Alterations in gut peptides involved in energy intake regulation through bariatric surgery

Ghrelin is produced primarily by the gastric antrum and fundus and, although the anterior section of the stomach is reduced in purely restrictive operations, there is some variation with respect to changes in ghrelin levels after surgical intervention. In some studies, lower fasting ghrelin levels were reported after laparoscopic sleeve gastrectomy (SG) [88,89]; while other findings showed increases in fasting ghrelin following LAGB [90–92]. A rise in ghrelin concentrations following



**Fig. 2.** Illustrations of restrictive procedures and Roux-en-Y gastric bypass. Reproduced with permission from Dr. Edward C Mun [171] A. Vertical banded gastroplasty; B. Adjustable gastric banding; C. Roux-en-Y gastric bypass.





**Fig. 3.** Illustrations of malabsorptive procedures. Reproduced with permission from Dr. Edward C Mun [171] A. Jejunioleal bypass; B. Biliopancreatic diversion; C. Biliopancreatic diversion with duodenal switch.

both AGB [93,94] and VGB [92,95,96], have been widely observed, but several studies have noted no change following either procedure [97–100], and two cross-sectional studies found a reduction in ghrelin concentrations following AGB, in comparison to BMI-matched counterparts [101,102].

Prospective and cross-sectional studies of ghrelin levels following RYGB have produced mixed results, with the majority showing a decrease in plasma ghrelin levels post bypass surgery [93,96,103,104]. Cummings et al. [11] in a cross-sectional study showed that ghrelin levels were considerably reduced after RYGB relative to both obese and normal weight controls. Higher levels of ghrelin were also measured in obese persons who had lost weight by dieting than prior to the diet [11], implicating a putative role for ghrelin in the adaptive response that limits the weight loss by dieting and enhances the likelihood of weight regain. Several researchers have since reported significantly lower levels of ghrelin in surgical patients who lost weight from RYGB in both cross-sectional and prospective studies [100,103,105,106]. The first few months following BPD also resulted in a significant reduction in ghrelin concentrations [100,101]. A post-surgical reduction of ghrelin may contribute to the persistent weight loss reported in obese patients following gastric bypass and mixed malabsorptive procedures. However, a number of studies demonstrated no significant change in ghrelin levels following gastric bypass [97,107] and BPD [108], or even higher ghrelin concentrations following both RYGB [109–111] and BPD [112–114].

Discrepancies among these results may be partially attributed to variation in the types of surgical and control groups chosen. In a prospective study, Faraj et al. [115] showed increased ghrelin concentrations in post-RYGB surgical patients undergoing weight loss but did not include a control group. Despite the increase in ghrelin levels observed in the surgical patients, they were still lower than levels reported in normal weight or comparably obese participants from other studies [11,116]. Similarly, another group found an increase in ghrelin at 12 months following gastric bypass that was comparable to BMI-matched controls [117]. A rise in ghrelin may have been anticipated following significant weight loss in these RYGB patients; however, if the postsurgical cohort were compared to BMI-matched controls that had lost weight conventionally, one might have expected a relatively lower ghrelin level in the operative patients.

Variation in surgical technique and hormonal assays may also be contributing factors in the differences reported in the literature. Thaler and Cummings [118] proposed that the inconsistencies across findings may be related to the integrity of autonomic vagal innervation. Vagal innervation influences ghrelin levels [14,82,119], and the degree to which the innervation is preserved is likely to differ between surgeons. In addition, the accuracy of commercial ghrelin assays used in the vast majority of studies has been raised [99].

Although it is not clear what the source of the variance is among studies, the type of surgical procedure seems to have a major influence on ghrelin levels. The overall reduction in postsurgical ghrelin levels in gastric bypass may contribute to the greater weight loss relative to other procedures, such as AGB [11,120].

Changes in PYY levels following bariatric surgery are under further investigation, and although inconsistencies still remain, the majority of evidence to date show that both restrictive [121–123] and malabsorptive [97,105,124] operations lead to a rise in fasting and postprandial PYY. Basal and postprandial PYY levels in morbidly obese surgical patients after VGB, were similar to non-obese participants in cross-sectional studies at 6 months, and were reasonably stable at 12 months post-surgery [123]. Comparable postprandial PYY<sub>3–36</sub> levels were also observed in post AGB patients and lean controls in two studies [102,125]. Korner et al. [126] showed an early postprandial rise in PYY concentrations in 12 patients in a cross-sectional study at 15–17 months post-RYGB. Garcia-Fuentes et al. reported that BPD produced a more substantial rise in PYY levels than RYGB in 29 morbidly obese patients [108]. Following RYGB, increases in postprandial PYY have been reported [88,127] and may be due to the absence of a functional pylorus and/or a significant portion of the stomach and pylorus being bypassed resulting in a faster emptying rate into small bowel. Higher PYY concentrations may lead to an early sense of satiety and reduced meal size, and together with reduced ghrelin may contribute to weight loss [88,128]. PYY inhibits ghrelin-sensitive neurons in the arcuate nucleus of the hypothalamus in a dose-dependent manner [129]. A change in the PYY to ghrelin ratio supporting PYY's anorectic action after bariatric surgery may result in deactivation of appetite centers centrally regulated by ghrelin. Longitudinal neuroimaging studies are needed to examine changes within the same individual pre and post-surgery and across different operations to clarify these points further.

Studies of post-operative changes in GLP-1 suggest that malabsorptive operations lead to a rise in fasting and postprandial GLP-1 concentrations [97,124,130–132]. Two studies have reported no postsurgical change in GLP-1 following AGB [97,98]. In contrast Reinehr et al. [121] reported lower GLP-1 levels in AGB patients at two years post-surgery. On the other hand, an increase in GLP-1 has been reported in one study [122] following SG. GLP-1 levels during an oral glucose tolerance test were increased in VGB and BPD, with a greater increase in BPD relative to VGB [130]. GLP-1 is produced from the distal small intestine; therefore a reduction in stomach size would not be expected to affect circulating levels of GLP-1.

Findings regarding changes in fasting GLP-1 levels after RYGB surgery are also mixed [121,127], but most report higher postprandial levels post-surgery in RYGB [97,105,131,133]. In one study, significant increases in GLP-1 levels were found six weeks following RYGB, when

patients were still severely obese [124]. Elevated levels of GLP-1 may contribute to the sustained efficacy of RYGB as well as improve and resolve diabetes, consistent with the incretin effect on weight and glucose metabolism [134]. RYGB restricts the stomach and bypasses the duodenum, which facilitates the rapid delivery of food contents through the GI tract, augmenting the release of GLP-1. It has been hypothesized that the increase in hypothalamic satiety signals (e.g. from GLP-1) may play contribute to the postsurgical weight loss observed after malabsorptive procedures [124,135].

Conflicting postsurgical changes in CCK have also been found in both restrictive and malabsorptive bariatric operations. Kellum et al. [136] measured CCK levels after a glucose or protein meal before and after RYGB and VBG, and the CCK response was not altered by either intervention. However in another study, Foschi et al. [95] evaluated patients before and after VBG surgery with healthy lean volunteer controls and showed that post-VBG patients had a more significant peak CCK response to an acidified meal known to enhance CCK production [137] and a faster time to the peak than controls, without differences between baseline CCK concentrations [95]. While a decline in CCK following RYGB might be predicted due to the diversion of ingested food contents away from the duodenum, the jejunum also secretes CCK [138]. In rats, CCK was not significantly altered after RYGB-induced weight loss [27]. CCK is primarily important for short term control of appetite and satiety [139] and unlike leptin and insulin [140], CCK does not appear to have an autonomous role in the long-term regulation of energy balance and body weight [141]. CCK can work synergistically with leptin to promote short term reduction of food intake in mice [142]. More research is needed to determine CCK's role in human obesity and the changes following bariatric surgery.

Several studies have demonstrated a significant decline in plasma leptin levels after bariatric surgery in relation to fat loss, irrespective of the surgical intervention [92,97,100,110]. A reduction in postprandial leptin levels were found in post VBG surgical patients in comparison to the baseline pre-operative state [143]. Lower leptin concentrations were seen at 2 and 12 months post BPD as compared to pre-surgical levels [113]. Serum leptin concentrations were also reduced in morbidly obese patients that underwent BPD-DS [144,145]. Rubino et al. [146] measured reduced leptin levels in post-RYGB patients as compared to non-surgical weight loss controls. Recent evidence suggests that leptin replacement therapy may aid in weight loss maintenance [68].

The impact of bariatric surgery on insulin levels and insulin resistance in obese persons is profound. In the bulk of restrictive bariatric operations, insulin tends to fall in postsurgical obese patients [92,97,100,110]. Reduced insulin concentrations were maintained at two years post GB and VBG [92]. Obese patients had decreased insulin levels after LAGB than BMI-matched controls [147]. Weight loss, resulting from gastric bypass and BPD, improves insulin resistance [100,132,148,149]. Insulin levels and resistance were also significantly lowered and improved respectively in post-operative obese patients with and without Night Eating Syndrome five months after RYGB [150]. Metabolic operations are being further investigated as an alternative to pharmacological agents in the treatment of diabetes. See Table 1 for a brief summary of changes in major appetite-related peptides secondary to RYGB surgery.

## 6. Alterations in neural activation through weight loss and bariatric surgery

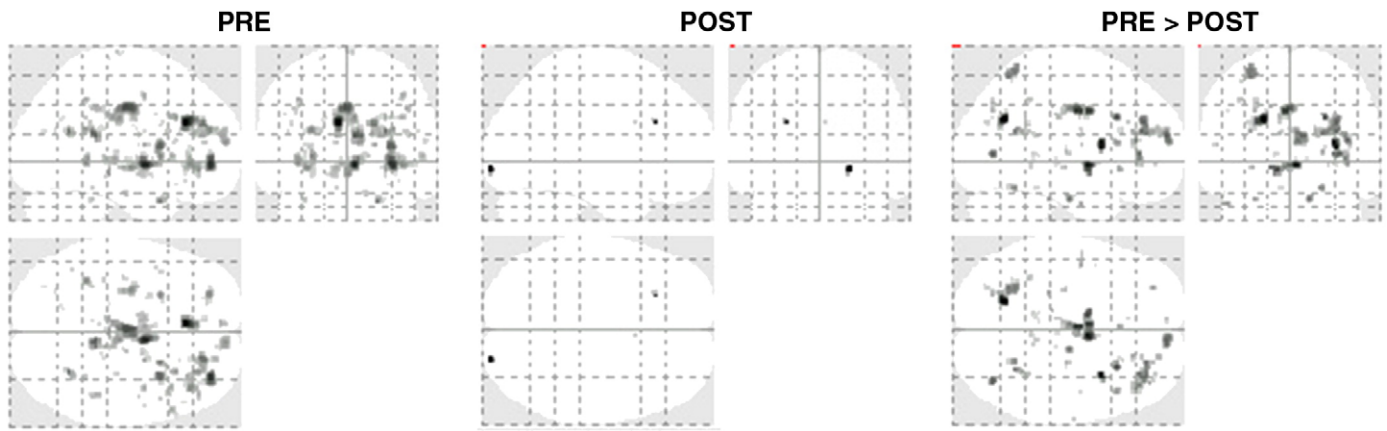
The majority of studies in this area are cross-sectional (e.g., lean vs. obese) and show differences in brain activation that suggest obese individuals may experience greater reward-related (predominantly mesolimbic) activation in response to appetitive stimuli [151–153] and food intake (e.g. [68,154]). There is, however, controversy surrounding this hypothesis [153] and it remains unknown whether any such lean vs. obese differences are cause or consequence of an

obese state, as very few longitudinal studies have been conducted. Despite radical postsurgical alterations in gut peptide signaling and established interactions between gut peptides and the neural control of food intake, there has been only one study of changes in brain receptor site binding [155] and one investigation of changes in neurological responses to food stimuli following bariatric surgery [156]. The limited available studies of the effect of weight loss and bariatric surgery on brain activation discussed below may provide insight and hypotheses for future investigations.

Although cross-sectional, comparisons between obese and weight-suppressed individuals, who may be prone to weight gain [157,158], may provide some insight into the association between weight loss and neural activation in response to appetitive stimuli and/or food intake. Cornier et al. [159] found greater hypothalamic activation in response to palatable food cues in lean individuals after a controlled five-day eucaloric diet relative to after 2 days of 30% overfeeding, suggesting an association between energy stores and hypothalamic activity in response to appetitive cues. This may reflect down-regulation of hypothalamic activity in lean individuals in response to appetitive cues upon entering a state of positive energy balance. Reduced obese (obesity-prone) individuals, however, did not show the same attenuation of hypothalamic response to food cues as lean individuals upon entering the same overfed state, suggesting an impaired interaction between appetitive stimuli and the homeostatic regulation of energy intake [159]. Although speculative, the absence of a decrease in hypothalamic activation in response to appetitive stimuli upon entering an overfed state may contribute to more or sooner resumption of 'homeostatic-based' eating [159]. In addition, impaired attenuation of hypothalamic activity may also leave open the potential for hypothalamic up-regulation of reward-related activation [53,54], which may be consistent with evidence showing greater PFC activation in reduced-obese relative to lean individuals [160]. Although almost certainly an oversimplification, as different subregions within both the hypothalamus [161] and PFC [72,162] play different roles in the regulation of energy intake, this blunt framework may help formulate testable hypotheses regarding the interaction between homeostatic (hypothalamic) and hedonic systems in appetitive responsivity.

Other studies have directly assessed acute responses to food intake, which yield different conclusions than those proposed by Cornier and colleagues [159,160] who examined neural responses to appetitive stimuli, potentially reflecting differences between anticipated and consummatory reward processing [153]. For example, Del Parigi et al. [154] showed differences in reward-related activation in response to a meal between lean and obese participants but no differences between obese and formerly obese participants. The authors suggest that differential or "abnormal" neural responses to meal ingestion in obese relative to lean individuals persists following weight loss. Alternately, in a cross-sectional reanalysis of existing data, Le et al. [72], reported that formerly obese women who successfully achieved weight loss by diet and exercise and maintained their weight loss for 3 months had greater activation of the dorsolateral prefrontal cortex (dlPFC) in response to a meal than did obese women. The authors hypothesize that this difference is related to greater inhibitory or satiety-related activation, for which there is some support [72,154,163], although it is also possible that the increased dlPFC activation reflects greater reward processing [162,164].

In the only available longitudinal study of brain activation pre and post non-surgical weight loss, Rosenbaum et al. [68] reported changes in brain activation in response to food cues following non-surgical weight loss (10% initial body weight) in 6 obese men and women. Following weight loss, leptin-reversible increases in activation were seen in the brainstem, parahippocampal gyrus, culmen, parahippocampal gyrus, inferior and middle frontal gyri, middle temporal gyrus, and lingual gyrus, while leptin-reversible reductions in activation were observed in the hypothalamus, cingulate gyrus, and middle



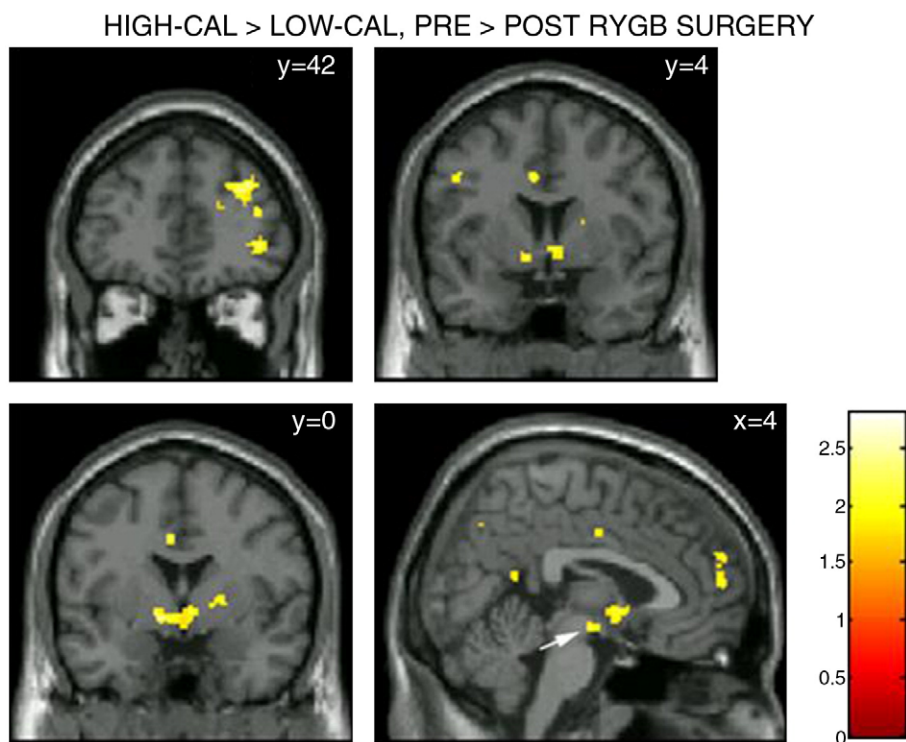
**Fig. 4.** Glass brain figure depicting brain activation in response to high-calorie relative to low-calorie food stimuli (high-calorie–low-calorie contrast) at  $p < 0.05$  uncorrected. A greater difference between mesolimbic dopaminergic pathway activation in response to high-calorie foods and mesolimbic dopaminergic pathway activation in response to low-calorie foods can be seen pre-relative to post-surgery. For display purposes, activation maps are shown without a cluster extent threshold.

frontal gyrus. Based on these results, the authors suggest that some changes in neural processing that may be associated with hunger and subsequent weight (re)gain may be leptin-reversible [68]. However, the complexity of these findings also illustrate the need for further controlled, hypothesis-driven research of brain activation in response to weight change before conclusions can be drawn about the interaction between brain systems (homeostatic vs. hedonic activation, weight change (gain vs. loss) and state of energy balance (positive vs. negative) in responses to appetitive stimuli.

Finally, two recent studies have examined the effect of bariatric surgery on neural activity. Using PET, Steele et al. [155] recently examined dopamine D2 receptor activity in five obese female subjects pre and six weeks after laparoscopic RYGB surgery. Five regions of

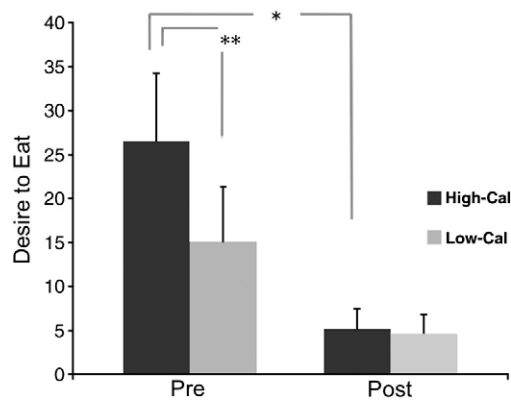
interest were studied (ventral striatum, anterior and posterior putamen, anterior and posterior caudate nucleus) and the researchers found that while baseline D2 binding in RYGB patients did not differ from non-obese controls, D2 receptor availability increased from pre to post-surgery, with the increase in receptor availability roughly proportional to the amount of weight lost. This suggests that the correction of diminished D2 binding in obese subjects (due to D2 receptor down-regulation) may play a role in appetite suppression and weight loss after RYGB.

The current authors used fMRI to investigate whether laparoscopic RYGB would result in significant changes in brain activation in response to high- and low-calorie food stimuli in 10 female patients. Given consistent postsurgical reductions in the desire for and intake of



**Fig. 5.** Coronal and sagittal slices depicting areas in which the difference between activation in response to high- and low-ED foods (High-ED–Low-ED Contrast) was greater pre-relative to post-surgery. Activation was considered significant at  $p < 0.05$  uncorrected, with an applied cluster extent threshold ( $k = 22$ ). The largest clusters ( $k > 80$ ) were seen in the dlPFC ( $y = 42$ ; top and cluster), ventrolateral PFC (vlPFC;  $y = 42$ ; bottom cluster), ventral striatum ( $y = 4$ ; bottom two clusters), putamen and lentiform nucleus ( $y = 0$ ; bottom cluster), and dmPFC ( $x = 4$ ; rightmost cluster). A nonsignificant cluster ( $k = 20$ ) was also observed in the VTA ( $x = 4$ ; white arrow). MNI coordinates are given in upper left corner of each panel. The color bar represents  $t$  values.





**Fig. 6.** The difference between the desire to eat following exposure to high-calorie relative to low-calorie foods (high-calorie-low-calorie) pre-surgery was greater than the nonsignificant high-calorie-low-calorie difference post-surgery  $p=0.007$ ;  $*p<0.05$ ;  $**p<0.01$ .

food [158,159], it was hypothesized that participants undergoing RYGB would show postsurgical reductions in mesolimbic reward pathway activation in response to food cues. It was also anticipated that postsurgical reductions in mesolimbic activity and desire to eat would be greater in response to high-ED relative to low-ED food cues given that presurgical preferences for foods high (vs. low) in fat and calories are typically reduced or eliminated following RYGB surgery [84,86]. Results revealed postsurgical reductions in brain activation in key areas within the mesolimbic reward pathway in response to food cues, which were significantly more pronounced in response to food cues that were high (vs. low) in caloric density (Figs. 4 and 5). These changes mirrored concurrent postsurgical reductions desire to eat following exposure to food cues that were high (vs. low) in caloric density (Fig. 6). These findings support the contention that RYGB surgery leads to substantial changes in neural responses to food cues encountered in the environment, provide a potential mechanism for the selective reduction in preferences for high-calorie foods, and suggest partial neural mediation of changes in caloric intake seen following RYGB surgery.

## 7. Conclusion

Obesity is linked to significant abnormalities in the neurohormonal control of energy intake, many of which have been elucidated by studies of gut peptides and brain activation in animals and humans. Yet there remains much work to be done in linking gut peptide and brain functions, particularly as they relate to energy balance. Although replication is needed, recent findings suggest that reward-related brain activation caused by exposure to appetizing food cues may be attenuated by elevations in PYY<sub>3–36</sub> and GLP-1, simulating a postprandial (fed) state [71,73]. In theory, these postprandial satiety signals are received by the hypothalamus [60], in turn down-regulating hedonic activation in the brain and reducing the likelihood or volume of subsequent food intake via reductions in perceived reward value [53]. However, despite putative attempts by the 'homeostatic' system to maintain energy balance, there is substantial evidence (particularly in obese individuals) to suggest that the hedonic system can override the homeostatic system and drive food intake even when sated if the perceived reward value is sufficiently high [41,61].

Surgical interventions for obesity, particularly RYGB, may lead to substantial and simultaneous changes in gut peptides [10], brain activation [155,156], desire to eat [156] and taste preferences [83]. Thus, the effects of bariatric surgery on the neurohormonal regulation of energy intake provides a tantalizing 'natural' experiment with which to explore gut-brain interactions [165,166], with an increasing number of studies suggesting that postsurgical changes within the neurohormonal system may account for a proportion of postsurgical

weight loss [8,167]. For example, postsurgical reductions in ghrelin and earlier and enhanced postprandial elevations of PYY and GLP-1 may reduce hunger and promote satiety [168]. The success of combination, relative to purely restrictive, procedures suggests that hormonal alterations may contribute to weight loss [167]. Relative to changes in gut peptides, very little is known about changes in brain activation following bariatric procedures. Investigations of non-surgical weight loss support an increase in reward-related/hedonic activation in response to appetitive cues [68,72,154,163], which could help explain weight regain in dieters. In contrast, the absence of an increase in desire to eat following RYGB, even on exposure to highly palatable food cues [84,122], is striking, and consistent with systemic changes in neural responses to food cues.

Interactions between postsurgical changes in gut peptides and neural activity have been widely proposed, but remain to be explicitly tested. Investigations of neurohormonal changes in RYGB may assist in developing non-surgical interventions to treat obesity and related comorbidities, which could serve as a viable treatment alternative for obese individuals who do not have access or do not qualify for bariatric surgery. Pharmacological activation of the hedonic network in animals, already fed beyond satiety, produces hyperphagia and preferentially increases the intake of foods high in fat and sugar [169,170]. Thus, identifying the actions of RYGB on gut-brain signaling may make it possible to develop pharmacological agents to increase satiety, and reduce hunger and preferences for high-ED foods.

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