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Changes in neurohormonal gut peptides following bariatric surgery

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Abstract

The rising prevalence of obesity has reached pandemic proportions, with an associated cost estimated at up to 7% of health expenditures worldwide. Bariatric surgery is currently the only effective long-term treatment for obesity and obesity-related co-morbidities in clinically severely obese patients. However, the precise physiological mechanisms underlying the postsurgical reductions in caloric intake and body weight are poorly comprehended. It has been suggested that changes in hormones involved in hunger, food intake and satiety via the neurohormonal network may contribute to the efficacy of bariatric procedures. In this review, we consider how gastrointestinal hormone concentrations, involved in appetite and body weight regulation via the gut–brain axis, are altered by different bariatric procedures. Special emphasis is placed on neurohormonal changes following Roux-en-Y gastric bypass surgery, which is the most common and effective procedure used today.

Keywords

brain; hormone; RYGB; ghrelin; GLP-1; PYY

Introduction

Obesity continues to increase in prevalence globally and is associated with the metabolic syndrome as well as chronic diseases, such as diabetes, hypertension and heart disease.[1] The etiology of obesity is multifactorial, and levels of appetite-related gut peptides have been shown to be related to body weight.[2] With the increase in obesity and the associated morbidity and mortality, research into the contribution of hormones involved in energy homeostasis and metabolism has also increased in recent years. As the number of bariatric procedures has risen concurrently with the rise in severe obesity, greater attention is being paid to how such procedures may affect appetite-related hormones, which is the focus of this review.

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Conflict of interest
The authors declare no conflict of interest.

Appetite control and feeding behavior are regulated in part by hormones released from the gut that activate areas of the brain primarily located within the limbic and mesolimbic systems.[2] Along with other areas within the dopaminergic reward pathway, the hypothalamus has been extensively linked to the control of food intake and energy homeostasis.[3] The hormonal signaling network, which provides information to the brain (primarily the hypothalamus) about energy stores and metabolic status includes leptin from fat stores and insulin from the pancreas as well as cholecystokinin (CCK), glucagon-like peptide-l (GLP-1), peptide $YY_{3–36}$ ($PYY_{3–36}$) and ghrelin from the gastrointestinal (GI) tract. Ghrelin is known to stimulate appetite whereas cholecystokinin, GLP-1 and $PYY_{3–36}$ promote satiety. Adipose tissue provides hormonal signals via leptin and insulin to the brain about energy stores, and likely from adiponectin and resistin.[4] Enterokines from the gastrointestinal tract and adipokines from fat work together to regulate short- and long-term food intake, respectively.

Surgical intervention for weight loss

Relative to behavioral interventions, surgical interventions produce greater weight loss in both the short and long term.[5] The currently employed surgical interventions for obesity all contain a restrictive component, limiting the amount of food that can enter the stomach pouch. Several procedures, most notably Roux-en-Y gastric bypass (RYGB), also contain a malabsorptive component, in which the bowel length is shortened, decreasing nutrient and calorie absorption. However, there is some question as to the degree and durability of postsurgical malabsorption associated with these procedures.[6] A number of studies have attempted to assess the mechanisms that lead to postsurgical reductions in body weight and associated medical comorbidities, which can occur before significant weight loss. The majority of these studies implicate postsurgical changes in appetite-related hormone levels.[5]

The reduction in caloric intake seen following bariatric surgery is likely due to more than just the physical changes made to the gastrointestinal tract.[7] However, the precise mechanisms of action are not well understood, particularly with RYGB.[8] An increasing number of studies suggest that postsurgical changes within the neurohormonal system may account for a proportion of postsurgical weight loss.[9] Gastrointestinal hormone levels are often altered following bariatric procedures and may contribute to postsurgical reductions in caloric intake and body weight. For example, postsurgical reductions in ghrelin, and earlier and enhanced postprandial elevations of PYY and GLP-1, may reduce hunger and promote satiety.[10] Recent evidence also suggests that postsurgical changes in such hormones may lead to changes in brain activation in response to appetitive cues.[11]

Surgical techniques

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. Vertical banded gastroplasty (VBG) and adjustable gastric banding (AGB) are examples of purely restrictive procedures. In VBG, the cardia of the stomach is sectioned off by a longitudinal staple line with a tight outlet wrapped by a band or mesh (Figure 1a). Adjustable gastric banding, on the other hand, partitions the upper stomach using a tight, adjustable, prosthetic band (Figure 1b). Laparoscopic adjustable gastric banding (LAGB) has progressively replaced VBG as the most commonly performed purely restrictive bariatric procedure due to its simplicity and lower complication rate.[12] Other restrictive procedures include sleeve gastrectomy, intragastric balloon, and endoluminal gastroplasty.

Malabsorptive procedures are primarily designed to bypass a portion of the small intestine, reducing the efficiency of nutrient absorption. The jejunoileal bypass is an example of a purely malabsorptive procedure, which consists of dividing the jejunum near the ligament of

Treitz and reconnecting it near the ileocecal valve, bypassing a long small bowel segment (Figure 2a). However, this procedure is no longer performed due to significant complications and relatively greater need for revision surgeries.[13]

A combination of restrictive and malabsorptive techniques is employed in several procedures, including the biliopancreatic diversion (BPD), biliopancreatic diversion with duodenal switch (BPD-DS) and RYGB. With the BPD procedure, there is a partial gastrectomy with a gastroileostomy or gastrojejunostomy, where a short bowel channel is attached to a long Roux-Y limb for nutrients and biliopancreatic secretions to be absorbed (Figure 2b). The BPD is also limited in use due to adverse health outcomes related to essential nutrient malabsorption.[14] The BPD-DS is a partial sleeve gastrectomy with an intact pylorus and a Roux limb with short bowel channel (Figure 2c). This procedure may be attractive to super-obese patients (BMI>50 kg m^{-2}), as it typically leads to relatively large postsurgical weight loss; however, it is not commonly performed due to adverse health outcomes similar to those seen in BPD.[13] Lastly, RYGB surgery is the most common bariatric procedure performed today, accounting for approximately 65% of all procedures worldwide.[15] With this operation, a small gastric pouch is created and connected to a short Roux-en-Y alimentary limb of distal small bowel, which is anastomosed to the jejunum, bypassing the duodenum and proximal jejunum (Figure 1c).

Gut and peripheral hormones as key appetite regulators

Hunger and satiety are mediated through a complex interplay of neurological and hormonal signals.[2,3] The hypothalamus processes many of these signals in relation to nutrient and energy availability.[3] Neural communication takes place between the hypothalamus and other brain regions (including cortical areas), which send effector responses to regulate food intake according to caloric need.[3,11,16] There are three different sets of signals from the periphery responsible for providing this information: one from adipose tissue that exerts long-term regulatory mechanisms on food intake, and the other two from the GI tract, with orexigenic as well as anorexigenic properties that exert primarily short-term effects on food intake.[17] Afferent signals can also result from direct mechanical stimulation of the GI tract, such as gastric distension due to stretch and pressure in the stomach.[16,18]

Ghrelin is an orexigenic peptide that can send signals to the hypothalamus via blood circulation as an endocrine hormone, through vagal afferents containing ghrelin receptors, or via release within the hypothalamus.[19] Neuropeptide Y (NPY) and agouti-related protein-producing neurons in the arcuate nucleus of the hypothalamus are stimulated by ghrelin to increase food intake.[17] Other peripheral hormones have been shown to induce satiety signals that can act directly on the brain, indirectly via the vagus nerve, or by slowing gastric emptying. These satiety hormones include CCK, GLP-1 and PYY, which rise after meals, and can suppress food intake when administered peripherally or centrally.[17]

Gut and peripheral hormones in relation to bariatric surgery

The seeming inability of the rearrangement of gut anatomy to fully explain the sustained reductions in body weight and medical comorbidities seen following bariatric surgery has inspired a body of literature on postsurgical changes in appetite-related hormones. Gut peptides known to cross the blood–brain barrier and induce changes in neural activation are likely candidates to account for the currently unexplained effects of bariatric surgery.[8,9] Ghrelin, PYY, GLP-1, CCK, insulin and leptin are released in the periphery and act indirectly on the vagus nerve and/or directly on target areas of the hypothalamus.[20] Thus, this review focuses on recent literature reporting postsurgical changes in appetite hormones that have been linked to hypothalamic targets. Bariatric surgery can also alter the concentrations of other gut hormones such as gastrin, gastric inhibitory polypeptide,

serotonin, neurotensin and vasoactive intestinal peptide. However, these hormones do not have substantiated effects on food intake and will not be discussed.

Search/inclusion criteria for studies of gut hormones following bariatric surgery

A literature search was conducted between February 2009 and July 2010. Articles were collected from Medline, PubMed, PsychINFO and TRIP databases. Articles were also identified from UpToDate Inc. published research and reviews. Because the primary aim of this review was to examine changes observed in gut hormones from before to after bariatric surgery, only articles that included measures of gut peptides involved in appetite control were included. No restrictions in terms of participant randomization or blinding were placed on included studies, and no restrictions were placed on the year of publication; however, articles published after July 2010 were not included. Literature searches were conducted using various combinations of the following key words: adiponectin, amylin, appetite, appetite centers, appetite control, bariatric surgery, BPD, BPD-DS, body weight, CCK, duodenal jejunal bypass (DJB), food intake, gastric banding, gastric bypass, gastrointestinal hormones, GLP-1, ghrelin, gut hormones, hypothalamus, insulin, LAGB, leptin, metabolic surgery, neuroendocrine peptides, neuronal activation, obesity, oxyntomodulin, PYY, resistin, RYGB, and weight loss.

Ghrelin

Ghrelin is a potent appetite stimulator and an endogenous ligand for the growth hormone secretagogue receptor. It is mainly synthesized by the gastric antrum and fundus. Injection of ghrelin centrally in animals stimulates the release of the orexigenic neuropeptides NPY and agouti-related protein-producing neurons, most notably in the arcuate nucleus of the hypothalamus.[21] Ghrelin enhances gut motility and speeds gastric emptying.[22] Ghrelin concentrations peak before meals and fall sharply postprandially, and some data in humans implicate ghrelin's involvement in pre-meal hunger and meal initiation. Higher ghrelin concentrations are noted during fasting, hunger or negative energy balance states such as short-term starvation, cancer or anorexia.[22] Sustained ghrelin levels by infusion can induce adiposity in animals[23] and, thus, ghrelin may also have a role in the long-term regulation of body weight.

Reduced ghrelin levels are observed after feeding, during hyperglycemia, and in obesity.[24] Fasting ghrelin has been found to be 27% lower in obese as compared to normal-weight individuals,[25] and ghrelin concentrations rise following weight loss.[26] Despite having lower ghrelin levels, overweight, obese and insulin-resistant individuals often continue to gain weight. The lower fasting levels in obesity suggests downregulation of ghrelin in response to overeating or excess body weight.

In purely restrictive operations, the upper portion of the stomach is reduced, with varied effects on ghrelin levels depending on the type of procedure. Bohdjalian and colleagues[27] prospectively studied 26 patients who had sleeve gastrectomy and showed that ghrelin concentrations were reduced 12 months post-operatively and remained low during a 5-year follow-up. A reduction in fasting ghrelin was found in other studies after laparoscopic sleeve gastrectomy;[28–31] however, increases in ghrelin following LAGB have been reported.[28,32–34] Similar variations in results were noted after AGB and VBG (Table 1). The majority of studies report an increase in ghrelin following both AGB[28,32–35] and VGB.[34,36–38] However, nearly as many studies report no change following either procedure,[39–43] and two cross-sectional studies have reported lower ghrelin concentrations following AGB relative to BMI-matched controls.[44,45]

Inconsistent postsurgical changes in ghrelin have also been found in malabsorptive procedures (Table 2).

The majority of studies examining changes in ghrelin after RYGB report a decrease in postsurgical circulating ghrelin levels.[4,30,38,42,43,46–51] In a cross-sectional comparison, Cummings and colleagues[52] found that ghrelin levels were markedly reduced in post RYGB participants, as compared to both obese and normal weight control participants.

They also reported that obese participants who had lost weight by dieting had higher levels of ghrelin than they did before dieting,[52] suggesting that ghrelin may have a role in the adaptive response that limits the amount of weight lost by dieting and increases the likelihood of weight regain. Subsequent to Cumming and colleagues[52] findings, others have also reported significantly lower levels of ghrelin in patients who lost weight from RYGB in both cross-sectional and prospective studies.[30,38,42–44,46,47,53–56] Decreased ghrelin levels were also present within the first year following BPD in two reports.[42,44] These studies suggest that a postsurgical reduction of ghrelin may contribute to the sustained weight loss noted in obese patients following gastric bypass. However, a number of researchers have found no significant change in ghrelin levels following gastric bypass[31,35,41,57] and BPD,[50,58] and higher ghrelin concentrations have also been reported following both RYGB[4,48–50] and BPD.[25,59,60]

Variation in study results of ghrelin levels may be at least in part explained by differences in the comparison groups selected. Holdstock and colleagues[61] prospectively studied the effect of RYGB and found that levels of ghrelin increased at 12 months and were similar to BMI-matched controls. These RYGB patients underwent significant weight loss at 12 months, which would be expected to lead to a rise in ghrelin levels. Had these operative patients been compared to BMI-matched controls that had lost weight conventionally, one might have expected a relatively lower ghrelin level in the postsurgical patients. In a prospective study by Faraj and colleagues,[62] there was also a rise in ghrelin levels in patients following RYGB undergoing active weight-loss. However, there were no control participants, and, 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.[52,63]

Cummings and colleagues[64] suggest that the variance across findings may also be related to the integrity of autonomic vagal innervation. Vagal innervation affects ghrelin levels,[19,65–67] and the degree to which the innervation is left intact is likely to differ between surgeons. Despite the inconsistencies, several key trends are apparent. First, the type of surgical procedure seems to have a major influence on ghrelin levels. The majority of studies examining changes in ghrelin levels following RYGB report a postsurgical decrease, whereas the majority of studies following AGB report an increase (Tables 1 and 2). In RYGB, the stomach antrum, fundus and duodenum, where most of the production of ghrelin occurs,[68,69] are largely excluded. Thus, ingested nutrients have significantly less contact with ghrelin-producing cells in the stomach and duodenum, which may lead to an inhibition of ghrelin release. In contrast AGB, which results in little or no reduction in ghrelin (Table 1), does not exclude the fundus or duodenum from contact with nutrients. This explanatory hypothesis is consistent with Fruhbeck and colleagues[54] who showed decreased fasting concentrations after RYGB and an increase after AGB as well as following conventional comparable weight loss by diet in obese patients. The reduction in postsurgical ghrelin levels in gastric bypass may contribute to the greater weight loss relative to other procedures.[3,16]

It should be noted that although the majority of studies refer to total ghrelin, as described above, ghrelin has two major molecular forms: acylated ghrelin and des-acylated ghrelin.

Acylated ghrelin, which induces a positive energy balance and is suppressed post-prandially and by pharmacological hyperinsulinemia, was previously presumed to be the only active form in terms of endocrine function. However, des-acylated ghrelin makes up the vast majority of total ghrelin,[70] and there is increasing evidence in both animals[71] and humans[72,73] that des-acylated ghrelin may exert effects in opposition to those exerted by acylated ghrelin. In addition, hyperinsulinemic and hyperinsulinemic–hyperlipidemic clamp studies show suppression of des-acylated ghrelin, but no change in acylated ghrelin, suggesting that insulin regulation of ghrelin may be specific to des-acylated ghrelin.[74] Finally, recent evidence suggests that des-acylated ghrelin binds specifically to HDL whereas acylated ghrelin binds equally to all lipoproteins.[75] Precisely how these two distinct forms of the same peptide interact in the regulation of energy balance remains under investigation, but illustrate the need to examine all forms of appetite-related hormones in the body.

Peptide YY

Although ghrelin has received the majority of the attention in surgically induced weight loss studies, there has been a shift in focus toward other hormones, such as PYY and GLP-1. In contrast to ghrelin, which is an appetite-stimulating hormone, PYY is a lower gut-derived hormone with anorectic effects.[17] It is secreted from intestinal L-cells in amounts that generally correspond to the energy ingested; however, the amount secreted may vary depending on the macronutrient content of the ingested energy.[76,77] PYY circulates in two forms: $PYY_{1–36}$ (total) and $PYY_{3–36}$ (referred to as ‘active’), with the latter being the major subtype found in the circulation.[78] $PYY_{1–36}$ binds to Y1–Y5 receptors,[79] and there is contradictory evidence on the effect of $PYY_{1–36}$ on food intake.[80–82] However, administration of $PYY_{3–36}$ reduces food intake over the short term in both animals[78,83] and humans.[84] $PYY_{3–36}$ likely reduces food intake by acting on Y2 receptors on vagal afferents, which results in increased activity in the arcuate nucleus of the hypothalamus to inhibit NPY activation.[85] Appetite suppression by $PYY_{3–36}$ may also result from slowing of gastric emptying (ileal brake mechanism).[86]

Levels of $PYY_{3–36}$ are low during fasting and peak 1–2 h following food intake, with high fat foods resulting in the greatest release of $PYY_{3–36}$.[87] Batterham and colleagues[84] demonstrated lower premeal $PYY_{3–36}$ levels in 12 obese as compared to 12 lean participants, as well as a smaller postprandial rise, suggesting that obesity may be associated with a $PYY_{3–36}$ deficiency. However, Pfluger and colleagues found no significant difference in fasting PYY levels between 66 lean and 63 obese subjects.[88] Nevertheless, obese participants remain sensitive to the anorectic effects of exogenously administered $PYY_{3–36}$.[89]

The majority of evidence suggests that restrictive procedures lead to a rise in fasting and postprandial PYY.[29–31,90–92] Fasting and postprandial PYY levels in clinically severely obese surgical patients were comparable to non-obese controls, following VBG in cross-sectional studies at 6 months and remained relatively constant at 12 months post-surgery.[91] Two studies have reported similar postprandial $PYY_{3–36}$ levels in post AGB patients and lean controls.[45,93]

Malabsorptive operations consistently demonstrate a post-surgical increase in fasting and postprandial PYY levels.[30,31,41,51,57,90,92,94] In a cross-sectional study at 15–17 months post-RYGB, Korner and colleagues[95] found an early postprandial rise in PYY concentrations in 12 patients. In a longitudinal study,[41] PYY levels were significantly greater in RYGB patients than in LAGB patients after 52 weeks, despite little difference in BMI’s between the two post surgical groups. The mechanism of this early and exaggerated response may be due to the stomach and pylorus being bypassed, which likely leads to faster

transit to the lower gut. Garcia-Fuentes and colleagues[50] found that BPD produced an even greater rise in PYY levels than RYGB.

An increase in postprandial PYY concentrations alone may result in an early sense of satiety and reduced meal size, and the combined effect of increased PYY and reduced ghrelin (Tables 1 and 2) may contribute further to weight loss.[31,55] PYY suppresses a high proportion of ghrelin-sensitive neurons in the arcuate nucleus of the hypothalamus in a dose-dependent manner.[96] A shift in the ghrelin/PYY ratio in favor of PYY after bariatric surgery may result in reduced appetite. Further longitudinal investigations pre and post surgery and across different operations are needed to clarify this point.

Glucagon-like peptide 1

Glucagon-like peptide-l is a key incretin hormone co-released with PYY from the distal intestinal L-cells of the gut after a meal. It is secreted in two equally potent forms, GLP-1 (7–37) and GLP-1 (7–36).[97] The primary functions of GLP-1 include the potentiation of glucose-stimulated insulin secretion, enhancement of β-cell growth and survival, inhibition of glucagon release, and control of food intake.[98] Following peripheral administration of GLP-1, most studies in humans report decreased food intake and increased fullness.[99] GLP-1 acts as an ileal brake for the upper GI tract and reduces food intake in part by slowing gastric emptying, resulting in greater gastric distension. Plasma levels of GLP-1 are higher both before and after food intake in lean as compared to obese individuals, who have lower fasting GLP-1 and an attenuated postprandial release.[100] Relatively few studies have examined changes in GLP-1 concentrations in obese patients after restrictive bariatric procedures. With respect to AGB, two studies have reported no postsurgical change in fasting GLP-1.[39,41] However, Reinehr and colleagues[90] found that fasting GLP-1 was reduced in AGB patients at 2-year post-surgery. Conversely, an increase in fasting and postprandial GLP-1 has been reported in one study[29] following sleeve gastrectomy. Other investigators showed that GLP-1 levels during an oral glucose tolerance test were increased in VBG and BPD, with a greater increase in BPD relative to VBG.[101] GLP-1 is secreted from the distal small bowel; therefore restriction of the stomach would not be expected to have a major impact on circulating levels of GLP-1.

Postsurgical increases in postprandial GLP-1 have been documented following malabsorptive operations.[30,31, 41,51,57,94,102,103] Morinigo and colleagues[94] found that RYGB leads to a significant increase in postprandial GLP-1 levels 6 weeks postoperatively, when participants were still markedly obese. Elevated levels of GLP-1 may contribute to the sustained efficacy of RYGB as well as improve and resolve diabetes, consistent with the mechanisms underlying this incretin's effect on weight and glucose metabolism.[104] RYGB reduces the size of the stomach and bypasses the duodenum, which allows for faster delivery of food contents through the gut,[105] enhancing GLP-1's effect. Dramatic increases in GLP levels have been observed immediately after RYGB,[94] which may be due to foregut exclusion and/or rapid hindgut delivery.[104] Long term follow-up with bariatric surgical patients may be informative about whether treatment with GLP-1 analogs for diabetes is sustainable. As with $PYY_{3–36}$, it has been suggested that increased hypothalamic satiety signals resulting from increases in postprandial GLP-1 may contribute to some of the postsurgical weight loss following malabsorptive procedures.[94,106]

Cholecystokinin

Cholecystokinin, an endogenous peptide hormone present in the gut and the brain, helps control appetite, ingestive behavior, and gastric emptying via both peripheral and central mechanisms. CCK is also known to have a number of effects on physiological processes including anxiety, sexual behavior, sleep, memory and intestinal inflammation.[107] CCK is

actually a collection of hormones labeled according to number of amino acids (for example, CCK 8 in the brain, CCK 33 and CCK 36 in the gut); however, differential effects on human energy balance have not been well established. Therefore, in keeping with convention, we refer to CCK in the singular. CCK originating from the gut is rapidly released from the duodenal and jejunal mucosa in response to nutrients, peaks at about 15–30 min and remains elevated for up to 5 h postprandially.[108] It is a potent stimulator of pancreatic digestive enzymes and bile from the gall bladder.[17] It delays gastric emptying and promotes intestinal motility. As a neuropeptide, CCK activates receptors on vagal afferent neurons, which transmit satiety signals to the dorsomedial hypothalamus. This action suppresses NPY and provides feedback to reduce meal size and meal duration.[109]

Studies of postsurgical changes in CCK are sparse, and the interpretation of early studies is somewhat hampered by difficulties associated with previous assay techniques due to low plasma concentrations, extensive molecular heterogeneity and close homology of CCK to gastrin, which circulates in higher concentrations.[110] Reported changes following bariatric surgery are variable in both restrictive and malabsorptive procedures (Tables 1 and 2). One study compared CCK levels after a glucose or protein meal before and after RYBG and VBG, and the CCK response was not affected by either procedure.[111] However in another study, Foschi and colleagues[112] compared patients before and after VBG surgery with healthy lean volunteer controls and found that post-VBG patients had a higher peak CCK response to an acidified meal known to increase CCK production[113] and a faster time to the peak than controls, without differences between baseline CCK concentrations.[112] In rats, CCK was not significantly altered after RYGB-induced weight loss.[109] However, Baldinger and colleagues[105] found a greater increase in CCK following RYGB in humans, as well faster emptying which are consistent as nutrients reaching the gut stimulate CCK. Although a reduction in CCK following RYGB might be expected due to the diversion of ingested food away from the upper part of the small intestine (the duodenum), the jejunum also releases CCK.[114]

In contrast to leptin and insulin,[115] CCK does not appear to have an independent role in the long-term regulation of energy balance and body weight,[116] but rather a primary role in short term control of appetite and satiety.[117] CCK can work synergistically with leptin to enhance short-term reduction of food intake in mice.[118] There is also novel work indicating that high insulin levels may increase circulating CCK via insulin-induced suppression of free fatty acids, with lipid infusion abolishing these effects.[119] As such, changes in macronutrient absorption after bariatric surgery affecting glucose- and protein-induced insulin secretion may contribute to altered circulating CCK levels, with potential effects on short-term satiety and gastric emptying. However, CCK's precise role in human obesity remains somewhat unclear, and more work is needed in examining changes in CCK following bariatric surgery.

Leptin

Leptin is produced primarily in the adipose tissue. It is categorized as an adipokine and plays a large role in the regulation of energy balance. Leptin produced from adipocytes sends signals about energy status from the periphery to hypothalamic regulatory centers.[17] In humans, serum leptin levels rise or fall in response to acute caloric surplus or deficits, respectively. Leptin administration has anorexigenic effects in both animals and humans,[17,20] although much less effective in humans.[120] Leptin also helps control adipose metabolism in the body by stimulation of lipolysis and suppression of lipogenesis.[121] Fasting serum leptin is higher in the obese due to the presence of more body fat, the main source of leptin.[121] Consistent with this, leptin decreases with weight and fat loss.[122] Following meals, leptin increases slowly and may make only a small contribution to short-term satiety, but a larger one to long-term body weight regulation.[123] Nevertheless, leptin

injections in obese humans have not been efficacious in reducing food intake and body weight, likely due to the development of leptin resistance.[123] It should be noted that leptin has also been found to be secreted from the gastric mucosa, but in much lesser amounts than from adipose tissue.[124] Although leptin secreted from adipocytes acts primarily on the hypothalamus for long-term regulation of food intake, gastric leptin is involved in the short-term regulation of digestion, including the delay of gastric emptying, absorption of nutrients by the intestinal wall and, the secretion of gastric, intestinal, and pancreatic hormones.[124]

As expected, fasting leptin levels consistently decrease[57] following bariatric surgery in relation to fat loss, irrespective of procedure.[4,25,34,35,37,39,41,42,59,62,125–130] Relative to pre-surgical levels, lower postprandial leptin levels have also been reported in obese patients after VBG.[131] A similar reduction was found at 2 and 12 months post BPD as compared to pre-surgery.[59] Plasma leptin concentrations were also lower in clinically severely obese patients who underwent BPD-DS.[37,130] Finally, Rubino and colleagues[129] found that leptin levels were reduced following gastric bypass as with non-surgical weight loss.[37] Recent evidence suggests that leptin-replacement therapy may aid in weight loss maintenance.[132,133]

Insulin

Insulin is a pancreatic hormone that maintains glucose homeostasis and was the first identified adiposity signal. Insulin levels rise after a meal to optimize glucose use for energy. The excess glucose is converted and stored in the liver and muscle as glycogen, and as fat in adipose tissue. Insulin concentrations vary directly with adiposity, and visceral fat is negatively correlated with insulin sensitivity.[134] Fasting and postprandial insulin are higher in obese than in lean individuals.[135] Insulin can penetrate the blood–brain barrier and binds to receptors in the arcuate nucleus to decrease food intake.[136]

In addition to its interactive effects with other hormones mentioned above, insulin itself is a long-term regulator of body weight, and, in the majority of restrictive bariatric operations, insulin tends to fall in post-surgical obese patients.[34,41,42,126,137] Reductions in postsurgical levels of circulating insulin were maintained at 2-year post GB and VBG,[34] and obese patients had lower insulin levels after LAGB than BMI-matched controls.[138] Weight loss, secondary to gastric bypass and BPD, improves insulin resistance.[42,62,137,139,140] However, Korner and colleagues[95] showed that insulin levels were decreased in surgically treated obese women with RYGB in comparison to BMI-matched obese counterparts. Insulin levels and resistance were also significantly lowered in obese individuals with and without Night Eating Syndrome 5months after RYGB.[141] These operations are being further investigated as a potential treatment for diabetes as an alternative to pharmacological agents.[142]

Other gut hormones

Other gut signals that regulate body weight through stimulation of hypothalamic regions include but are not limited to pancreatic polypeptide,[143] oxyntomodulin,[144] adiponectin,[145] resistin,[146] and amylin.[147] Pancreatic polypeptide has structural similarities with PYY and NPY. It is secreted from pancreatic cells in relation to caloric ingestion and can remain in the bloodstream for up to 6 h postprandially. [148] It is also involved in gallbladder relaxation and inhibition of pancreatic secretion. Once secreted, the binding action of this enteroendocrine hormone to Y_4 receptors in the arcuate nucleus of the hypothalamus has been implicated in the suppression of food intake in mice.[143] Few studies have looked at pancreatic polypeptide following obesity surgery, but most show that bariatric surgery has only minimal influence.[29,39,48,149–154]

Oxyntomodulin (OXM) is co-secreted with GLP-1 from the enteroendocrine L cells to suppress the acid-producing oxyntic glands of the stomach.[155] Central injection of OXM reduces food intake and weight gain in rodents and has been shown to reduce hunger and food intake in humans.[156] Oxyntomodulin also has an incretin effect following glucose intake similar to GLP-1.[157] Central intravenous OXM infusions in the rat hypothalamus reduced food intake,[158] and intraperitoneal administration of OXM in rodents suppressed fast-induced and dark-phase food intake.[159] In one study, an increase in OXM precursor gene (pre-proglucagon) expression was observed after an ileal transposition in a ratmodel.[160] Levels of OXM increased in the majority of bypass operations, [57,111,161,162] whereas no significant changes in OXM levels were observed following VBG.[111]

Adiponectin is a peptide produced and released exclusively by adipose tissue, in this respect similar to leptin. However, plasma levels of adiponectin remain relatively constant throughout the day and are not affected by food intake.[17] Furthermore, there is a negative correlation between BMI and plasma levels of adiponectin.[4] Obese individuals with diabetes have even lower plasma levels of adiponectin than non-diabetic obese individuals,[4,42] which suggests that diminished adiponectin may contribute to insulin resistance. A dramatic increase has been found in adiponectin levels after RYGB in obese patients.[4,42,62,106,163] Adiponectin levels also increased after weight loss following a BPD-DS procedure.[37,130]

Resistin, also known as adipose tissue-specific secretory factor, is another adipokine hormone that acts on skeletal muscle myocytes, hepatocytes, and adipocytes. Opposite in effects to adiponectin, higher resistin may contribute to insulin resistance.[4] Resistin is positively correlated with obesity in animal studies,[164,165] but there is contradictory evidence about its role after weight loss induced by diet or surgery in humans.[4,163,166] Amylin, which is co-secreted with insulin from the pancreas, is considered a major satiety peptide, and was recently found to be decreased after a 12 kg weight loss following gastric bypass surgery in obese individuals.[51]

Discussion

Similar postsurgical changes have been found between restrictive and malabsorptive procedures in levels of leptin, insulin, and adiponectin, suggesting that these hormonal changes may result primarily from the associated weight loss.[41,42] Differences between these procedures in their effect on other appetite-related hormone levels that may contribute to the generally superior effectiveness of combination procedures over purely restrictive procedures are more difficult to assess, but in general show differences between procedural types on changes in ghrelin and GLP-1. Most studies show a postsurgical decrease in levels of the orexigenic hormone ghrelin following gastric bypass procedures,[38,42,43,46,47] but a postsurgical increase in ghrelin levels following gastric banding.[32,34,36–38,46] In addition, most studies of the anorexigenic hormone, GLP-1, reveal significant increases following bypass procedures [51,94,106,167,168] but no change following banding.[39,41,51] With regard to PYY, most studies show a postsurgical increase in postprandial PYY in malabsorptive[31,41,90,94] and some restrictive (VGB, sleeve gastrectomy)[29,91] procedures; however, it remains unclear whether AGB has any significant effect on postprandial PYY levels.[41]

These general findings suggest potential mechanisms by which bypass patients would experience less hunger, as well as greater and sooner postprandial fullness as compared to banding, thus contributing to greater weight loss. The bypassing of the stomach and upper intestine may promote faster gastric emptying. More rapid transit of nutrients through the lower gut may stimulate a faster and enhanced postprandial release of gut peptides, and enhance the effect of the ileal break mechanism.[7]

Roux-en-Y gastric bypass remains the most commonly performed and effective bariatric procedure used today; however, its mechanisms may be the least well understood. Recent evidence suggests that the restrictive and malabsorptive components alone are insufficient to account for the resulting weight loss.[7,8,169,170] Currently, sufficient data are not available to quantify the individual contributions to postsurgical weight loss of the restrictive and malabsorptive components of RYGB surgery. Through comparisons with VGB, it may be possible to crudely estimate the magnitude of postsurgical weight loss not accounted for by the restrictive mechanism in RYGB. The comparison with VGB was chosen over AGB, as VGB involves sectioning of the stomach (as opposed to banding) and the level of restriction in VGB may better approximate that of RYGB.[52,171]

In prospective randomized trials, 50–80% loss of excess body weight was seen 1–2 years following RYGB, as opposed to only 30–50% 1 to 2 years after VBG, suggesting that 0–50% (Low end point of range (0%) determined by subtracting the highest % excess body weight loss following VGB from the lowest % excess body weight loss following RYGB (50%−50%=0%). High end point of range (50%) determined by subtracting the lowest % excess body weight loss following VGB from the highest % excess body weight loss following RYGB (80%−30%=50%)) of the weight loss seen following RYGB may be left unexplained by the restrictive component. A meta-analysis comparing RYGB to VGB confirms that the short-term (1–2 years) disparity between procedures is approximately 25%,[172] suggesting that the restrictive component accounts for up to 75% of post-RYGB weight loss. However, longer-term data suggests a greater disparity between these procedures.[173] A nearly 80% failure rate (failure to maintain the loss of at least half of excess body weight) has been reported after 10 years with VGB,[12] and both cross-sectional and prospective studies suggest that the disparity between RYGB and VGB may increase over time due to the superior weight loss maintenance following RYGB.[169,171,174–176] In addition, it is important to note that estimating the effect of gastric restriction itself by comparisons with VGB would hold true only if weight loss seen following VGB were achieved independent of changes in gut peptides. However, several postsurgical changes in gut peptides have been noted following VGB, such as increases in postprandial $PYY_{3–36}$ [91] and GLP-1,[101] and may account for a proportion of postsurgical weight loss. Therefore, we feel it reasonable to estimate that the restrictive component may account for 50–75% of post-RYGB weight loss.

Although a clear effect of malabsorption can be seen in weight loss resulting from procedures such as jejunoileal bypass and BPD, clinically significant malabsorption, measured by indices such as albumin, prealbumin and fecal fat, is not observed after the standard proximal RYGB.[7,177–180] In addition, several animal studies[181–184] have shown that sleeve gastrectomy with ileal transposition, a new procedure designed to combine gastric restriction with intentional changes in gut peptide profile (earlier and exaggerated release of GLP-1 & PYY, lower ghrelin, etc.) while avoiding nutrient malabsorption, shows weight loss equal to that seen following RYGB. Initial studies in humans suggest similar findings with sleeve gastrectomy with ileal transposition. For example, Gagner *et al.*[185] reported that individuals undergoing sleeve gastrectomy with ileal transposition as a revision surgery of BPD-DS showed completely restored gut absorptive function while maintaining weight loss.

Rubino and Marescaux[186] found no reduction in food intake or body weight in rats undergoing gastrojejunal bypass, which involves a bypass of approximately the same amount of intestinal foregut as is excluded in RYGB but spares the stomach, as compared to sham-operated rats. Finally, malabsorptive effects of only 4% have been shown in animal models[187] and similarly modest effects have been postulated in humans.[7,35,181,188] Thus, a

rough estimate of 5% of weight loss attributable to the malabsorptive component of RYGB may be reasonable.

Together, the estimated percentages of post-RYGB weight loss attributable to gastric restriction (50–75%) and malabsorption (B5%) suggest that the restrictive and malabsorptive components combined account for approximately 55–80% of weight lost through RYGB. Thus, approximately 20–45% of post-RYGB weight loss may be currently unexplained. Increases in resting energy expenditure have been raised as a potential contributing mechanism.[187,189] However, evidence appears to indicate the REE decreases postsurgically in proportion to fat loss.[190,191] Similarly, dumping syndrome was proposed as an additional potential mechanism; however, severity of dumping syndrome correlates poorly with weight loss,[7] rendering it unlikely to play a significant role in the efficacy of RYGB. Therefore, an estimated 20–45% of weight loss secondary to RYGB surgery could be explained by other factors,[192] a large percentage of which may be attributable to the associated neurohormonal changes discussed in this review, leaving the potential open for substantial and sustainable weight loss effects if these neurohormonal effects can be identified and replicated pharmacologically.

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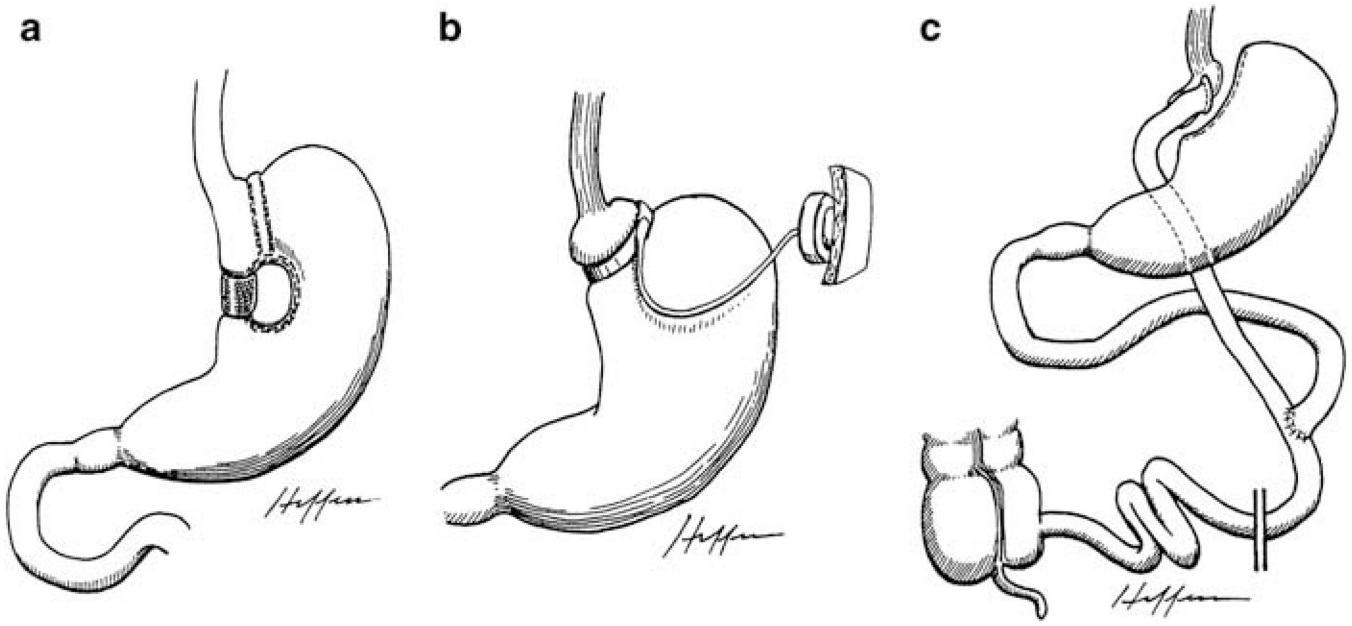

Figure 1.
Illustrations of restrictive procedures and Roux-en-Y gastric bypass. Reproduced with permission from Dr Edward C Mun.[173] (a) Vertical-banded gastroplasty; (b) Adjustable gastric banding; (c) Roux-en-Y gastric bypass.

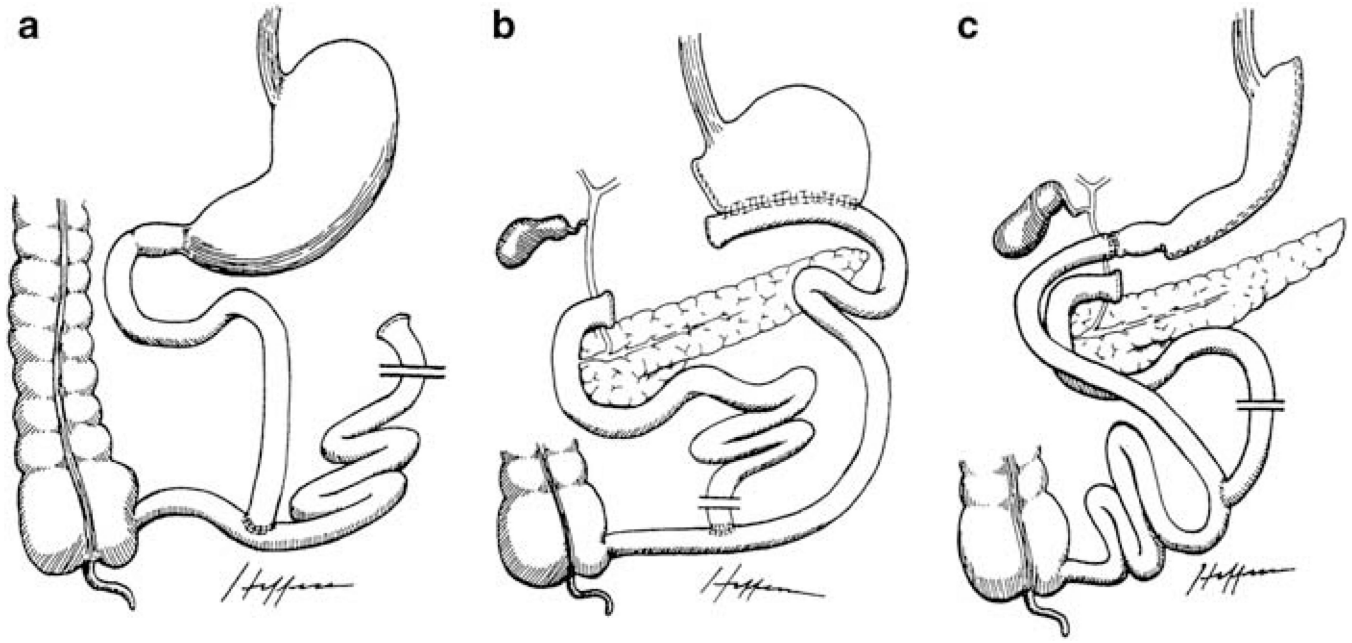

Figure 2.
Illustrations of malabsorptive procedures. Reproduced with permission from Dr Edward C Mun.[173] (a) Jejunoileal bypass; (b) Biliopancreatic diversion; (c) Biliopancreatic diversion with duodenal switch.

Table 1

Summary of GI hormone changes after restrictive surgical procedures

Hormone	Type of restrictive surgery		
	AGB[c]	VBG[d]	SG[e]
Ghrelin[a]	↑28,32–35	↑34,36–38	↓27–31
	↔39–41	↔42,43	
$PYY_{3–36}$[b]	↑45,193	↑91	↑92,126
GLP-1[b]	↔41,51	↑101	↑126
CCK[b]		↑112	↔126
		↔111	
Leptin[a]	↓34,35,39,41,125	↓34,37,42	↓126
Insulin[a]	↓34,41,137	↓34,42	↔126
	↔39		
PP[a]	↔39	↓152	↔126
		↔153	
OXM[b]		↔111	
Adiponectin[a]	↑125,128,194	↑37,42,196	↔126
	↔195	↔195	
Resistin[a]	↑195	↑195	↓126
Amylin[b]	↔51		↔126

↑ = postsurgical increase. ↓ = postsurgical decrease. ↔ = no significant postsurgical change.

[a] Fasting (*vs* postprandial based on relevance to peptide and majority of available studies).

[b] Postprandial (*vs* fasting).

[c] AGB = adjustable gastric banding.

[d] VBG = vertical banded gastroplasty.

[e] SG = sleeve gastrectomy.

Table 2

Summary of GI hormone changes after malabsorptive surgical procedures

Hormone	Type of malabsorptive surgery		
	GB[c] (JIB[d], RYGB[e], DJB[f])	BPD[g]	BPD-DS[h]
Ghrelin[a]	↑4,48–51	↑25,59,60	↓37,130
	↓30,38,42,43,47,197	↓42	
	↔31,35,41,57	↔50,58	
$PYY_{3–36}$[b]	↑30,31,41,51,57,92,94,102,103		
GLP-1[b]	↑30,51,57,94,103,106,167,193,198–200	↑101,140,199	
CCK[b]	↔111,129		
Leptin[a]	↓4,35,41,42,49,57,62,128,129	↓25,42,59	↓37,130
Insulin[a]	↓4,41,42,57,62,106,127,129,137,141,197	↓42,140	
	↔57,201		
PP[a]	↔48,150,151		
OXM[b]	↑57,111,151,161,162		
Adiponectin[a]	↑4,42,62,106	↑42,130	↑37,130
Resistin[a]	↔4,166		
Amylin[b]	↓51		

↑ = postsurgical increase. ↓ = postsurgical decrease. ↔ = no significant postsurgical change.

[a] Fasting (*vs* postprandial based on relevance to peptide and majority of available studies).

[b] Postprandial (*vs* fasting).

[c] GB = gastric bypass.

[d] JIB = jejeunoileal bypass.

[e] RYGB = Roux-en-Y gastric bypass.

[f] DJB = duodenal-jejunal.

[g] BPD = biliopancreatic diversion.

[h] BPD = biliopancreatic diversion. hBPD-DS = biliopancreatic diversion -duodenal switch.