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Review

Metabolic surgery and gut hormones – A review of bariatric entero-humoral modulation

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ABSTRACT

The global pandemic of obesity is increasing. Inappropriate food intake relative to energy expenditure results in increased adiposity. These factors are partly regulated by signals through the gut-brain and adipose-brain axes. Metabolic operations (otherwise known as Bariatric surgery) offer the most effective results for sustained metabolic improvement and weight loss. They modulate a number of gut hormones that constitute the gut-brain axis. This review summarizes the literature to-date reporting the gut hormone changes associated with these operations and their subsequent effects on appetite. Understanding the anatomical differences between each operation and how these can differentially regulate gut hormonal release can provide new treatments and targets for obesity, appetite and metabolic disorders.

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1. Introduction

Obesity has become a major contributor to the global burden of chronic disease, affecting virtually all ages and socioeconomic groups. Despite the application of a variety of traditional treatment therapies, including the promotion of good diet and exercise, the incidence of morbid obesity continues to rise, with a parallel increase in cardiac disease, and now not only affects the adult population but increasingly the paediatric demographic as well. This has led to focused research on introducing and refining an arsenal of obesity treatment modalities that recently has included bariatric surgery [1], an umbrella group of operations that are now also known as 'metabolic surgery'. This treatment for obesity has shown the best results for rapid weight loss, which improves multi-systemic morbidity and mortality rates, with a corresponding decrease of health-care costs [2,3].

The gastrointestinal tract is the largest endocrine organ in the body and it was through the discovery of gut hormones that the field of endocrinology initially developed. Bayliss and Starling first discovered 'Secretin' by demonstrating that an acidic infusion into a denervated jejunum led to pancreatic secretions, whilst a similar application of intravenous acid could not reproduce this [4]. Following the introduction of more advanced biochemical techniques in the 1960s, Secretin and a number of other gut hormones have been identified and now constitute the gastro-entero-pancreatic system. Many of these hormones have actions on the central nervous system and appetite, working through the so-called gut-brain axis. Of these, cholecystokinin (CCK) was the first hormone that was studied for its effect on satiety [5,6].

The involvement of the central nervous system in the pathogenesis of obesity has been clearly identified through the identification of genetic variants at the FTO [7] (fat mass and obesity associated) and MC4R [8] (melanocortin 4 receptor) loci. However, the purpose for this article is to review the association between bariatric surgery and the role of surgically modulated gut hormones in altering appetite.

2. Hormonal control of central appetite regulation

Both long and short-term peripheral hormonal signals can influence feeding and eating behaviour. The hypothalamus has an important role in the control of appetite, although other regions also carry out processing of signals to contribute to this regulation. These include the nucleus tractus solitarius and the area postrema.

Hormonal signals and neural signals are integrated to coordinate both feeding behaviour and energy balance. Long term signals are mainly humoral and include information regarding overall health, endocrine status and systemic energy store levels. Shorter term signals include gut hormones and neural signals from feeding centres in the brain, regulating meal initiation and termination [9].

An inappropriate energy balance or excessive eating behaviour will result in obesity as a result of a net increase in energy balance. This has been hypothesised to result from a rise of the brain's energetic "set-point" [10]. Under stable physiological circumstances, these set-points tend to only increase and can only be decreased by extreme stress situations such as starvation. Despite the development numerous pharmacological agents and lifestyle interventions, clinicians continue to find the epidemic of obesity a treatment challenge. Natural feedback mechanisms regulating these set-points include the gut-brain and the adipose-brain axes. The gut-brain axis consists of gut hormones (enterokines) and gut neuronal signals (including those from the from the vagus) [11] whereas the adipose-brain axis consists of adipose hormones (adipokines) [12] (Fig. 1). The most successful sustained weight-loss therapy to-date for morbid obesity is bariatric surgery [2]. These interventions have been demonstrated to significantly modulate

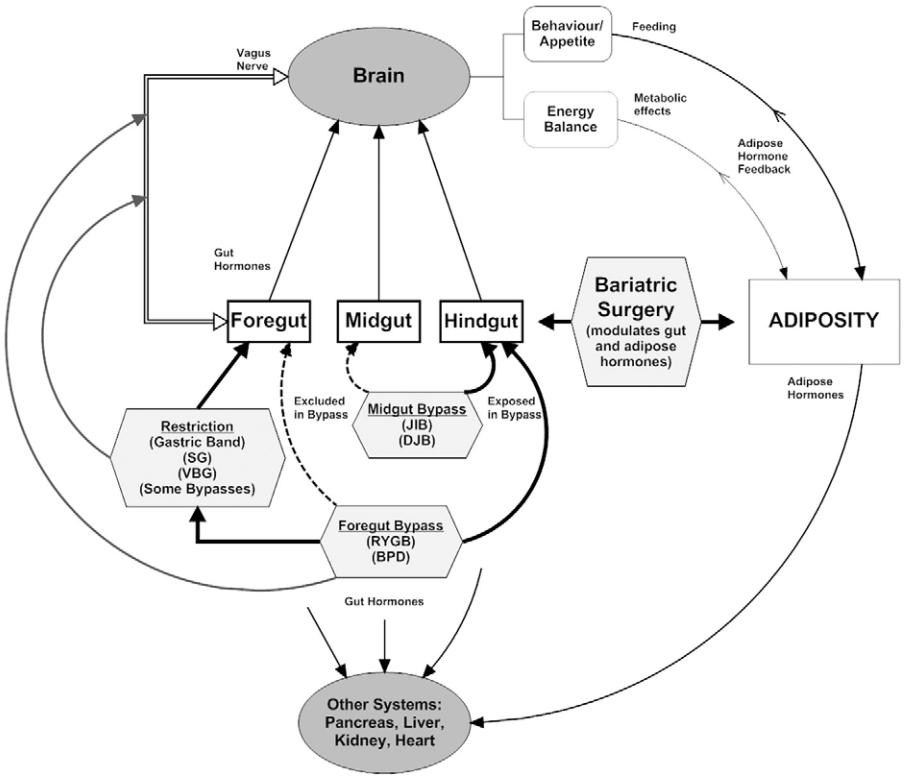

Fig. 1. The central regulation of appetite and energy balance leading to obesity, and the role of bariatric surgery in modulating gut and adipose hormones via the gut-brain and adipose-brain axes. Restrictive procedures (gastric banding, gastroplasty and sleeve gastrectomy) constrict the foregut, whereas foregut bypass procedures (gastric bypass and biliopancreatric diversion) exclude food from the stomach and duodenum (foregut) and therefore expose the hindgut. Midgut bypass procedures (jejuno-ileal bypass) exclude food from the jejunum and proximal ileum (midgut) also exposing the hindgut.

endogenous gut and adipose hormones to influence both energy balance and appetite.

3. Concepts in measuring gut hormones

Some gut hormones circulate as single peptides, whilst others are peptides of different lengths and amino acid patterns (such as gastrin). This requires the technique of radioimmunoassay to be directed, not only to one peptide, but also for plasma patterns characterized by a predominance of specific peptides that correspond to one hormone. Furthermore, it can also be useful to measure levels of biological precursors and processing intermediates to attain an increased diagnostic accuracy [13,14].

The reliability of measurements also requires peptide specific considerations such as identifying and controlling for variables that exist during sample collection, timing, processing, storage, calibration and bioassay. Sufficient methodological detail is not always available in the literature, and therefore communication and collaboration with well-informed researchers are essential.

4. Bariatric or metabolic surgery

The word 'bariatric' stems from the combination of two Greek words, namely 'baros' and 'iatrike' which combine to literally mean 'weight treatment'. The first procedures were derived independently in the mid-1950s by Arnold Kremen [15] and Richard Varco [16,17]. The subsequent use of 'bariatric surgery' designates an umbrella term to account for all surgical procedures that are used to help in the reduction of excess weight.

These operations are further subdivided by surgeons into three groups; restrictive surgery, pure bypass operations (or so-called malabsorptive surgery) and combinative procedures. Technically a fourth category would include other procedures such as jaw wiring and fat-debulking surgery that includes abdominoplasty, liposuction and omentectomy, although these are not generally considered as purely bariatric operations. They can however mildly reduce weight in their own right, and can be used in conjunction with more conventional bariatric procedures.

Restrictive surgery literally restricts or decreases the size of the stomach and causes reduced hunger or earlier satiety with smaller volumes of food. Procedures within this category include *gastric banding (GB)* where an adjustable band is placed below the cardia of the stomach to create a small upper gastric pouch. Alternative restrictive techniques include a *sleeve gastrectomy (SG)* – a newer procedure where literally a large 'sleeve' of stomach is resected leaving a small gastric tube with an intact pylorus. Older methods of restriction include *gastroplasty* which partitions the stomach with the use of a stapler (either horizontally or vertically), limiting the area of the stomach to which food enters. Both procedures can be performed laparoscopically and can be carried out concurrently as in a *vertical banded gastroplasty (VBG)*, where both banding and stapling take place.

Pure Bypass Operations or so-called 'Malabsorptive Surgery' was initially designed with the aim of decreasing the absorption of nutrients by excluding food from segments of the alimentary tract by either shortening tract length, bypassing anatomical segments of the gastrointestinal system, or even inter-transposing various segments of bowel. Examples of this are the first described bariatric procedure of *jejuno-ileal bypass (JIB)* [15], the *duodenojejunal bypass (DJB)* [18], and biliopancreatic diversion [19] with or without duodenal switch [20]. Although these procedures can successfully induce weight loss, the term 'malabsorptive' can be misleading as there is no clear evidence that 'malabsorption' accounts for the dramatic weight loss observed [21–23].

Combination surgery aims to join the benefits of both restrictive and malabsorptive procedures. Examples include *Roux-en-Y Gastric Bypass (RYGB)* [24,25]. Here a small stomach pouch is created by partial gastrectomy and subsequent anastomosis of the small stomach pouch to the jejunum (gastro-jejunostomy). Bypass is then achieved by identifying the transected stomach remnant and its attached segment of duodenum and proximal jejunum, which is then mobilized at the jejunal end (The Roux-en-Y limb), to be anastomosed to a distal segment of the jejunum to form a jejuno-jejunostomy. Chyme now passes from the small stomach pouch directly to the jejunum, bypassing a large area of the stomach and the duodenum. As a result RYGB procedure can be summarised to result from five components: (1) small stomach pouch, (2) bypassed stomach and proximal small bowel, (3) alterations in the flow of bile, (4) manipulation of the vagus nerve (that can vary) and (5) distal small bowel being brought more proximally and thus allow earlier contact with food.

Due to their dramatic effects on the resolution of diabetes, metabolic syndrome and the cardiovascular system [26,27], these procedures are now considered as metabolic operations, particularly as many of their metabolic actions occur before any noticeable weight loss [28]. Furthermore, the role of metabolic modulation in the actual process of weight loss itself has become increasingly recognised.

In 1975 it was revealed that gastrointestinal bypass operations could modulate some gut hormones [29,30]. Many of these surgically modulated hormones have anorectic actions, and their post-operative weight-loss effects can be significant, even when confronted with severe underlying metabolic dysfunction [31]. Not all bariatric patients achieve a 'good weight loss' as approximately 10–15% of gastric bypass patients have a 'poor weight loss' that is associated with a greater Body Mass Index, male sex, and diabetes [32,33]. This may represent a diminished gut hormone release or response, as increasing evidence demonstrates treatment with external gut hormones can augment weight loss, whereas gut hormonal blockade by antibodies or pharmacological agents (such as Octreotide) can diminish the weight loss seen in these operations [22].

5. Obesity classification and current indications for bariatric procedures

The National Institutes of Health (NIH), The American College of Surgeons (ACS), The Society of Gastrointestinal Endoscopic Surgeons (SAGES), The American Society of Bariatric Surgeons (ASBS) and the United Kingdom's National Institute for Health and Clinical Excellence (NICE) have similar guidelines which identifies patients who could be considered for bariatric surgery. In general bariatric surgery is indicated in morbidly obese patients (Body Mass Index (BMI)> 40 kg/m^2), or those with BMI>35 kg/m^2 who suffer with significant comorbidities. Surgery should only be considered in these patients in the event that non-surgical treatment has been unsuccessful, and that all patients are reviewed and followed up within in a multi-disciplinary specialist obesity unit.

In order to classify modulated gut hormones in this review, we have listed them according to the embryological site of their release: foregut, midgut and hindgut. This further allows us to consider each operation from a metabolic viewpoint (Fig. 1). Here restrictive procedures (gastric banding, gastroplasty and sleeve gastrectomy) constrict the foregut, whereas foregut bypass procedures (gastric bypass and biliopancreatic diversion) exclude food from the stomach and duodenum (foregut) and therefore expose the hindgut to altered chyme. Midgut bypass procedures (jejuno-ileal bypass) exclude food from the jejunum and proximal ileum (midgut) also exposing the hindgut to altered chyme.

6. Foregut hormones

6.1. Ghrelin

Ghrelin is a 28 amino acid peptide that is a peripherally active appetite stimulating hormone (Orexigen). It is released mainly from

the gastric epithelial cells, although there is also some expression in the pituitary gland [34]. Circulating levels are inversely correlated with body weight and rise following weight loss. Furthermore, levels rise during fasting and fall rapidly after a meal. Calorie intake appears to be a primary regulator of plasma levels, although circulating levels are lower in obese individuals, revealing a possible role to decrease food intake in this population [35,36].

This dual expression both within and outside the central nervous system has led to the identification of its dichotomous actions peripherally and centrally. Central injection of ghrelin results in a direct orexigenic action on the hypothalamus, whereas peripheral administration results in potent growth hormone secretion and the stimulation of food intake via the gut-brain axis. This is likely to take place through the vagus nerve, where the appetite stimulation can be abolished after vagotomy [11]. Parenteral nutrition can decrease levels, but does not alter hunger, suggesting a more complex role than of that of simply orexigen. Its actions also include glucose homeostasis and adipocyte metabolism [37,38].

The effects on appetite are mediated through the ARC of the hypothalamus by activation of NPY/agouti-related peptide neurons. It also mediates feeding behaviour through third ventricular and adjacent neurones. It is an endogenous ligand for the growth hormone secretagogue receptor (GHS-R), and binding requires a vital acyl side chain on a serine residue at position 3 [39].

The results of bariatric surgery in modulating Ghrelin have been controversial. Those studies involving foregut bypass (either gastric bypass or biliopancreatic diversion) (Table 1) reveal that of 42 studies, 50% revealed a decrease, 26% no significant change and 24% revealed an increase. Although it would have been expected that these operations would decrease hunger and therefore decrease ghrelin, this has not been the case. The studies that reveal an increase in ghrelin post-operatively still do not report a rise in levels seen in lean controls. Furthermore, a number of studies that report a decrease do so by quoting the immediate drop of ghrelin post-operatively in a physiological state of surgical stress. The longer-term studies tend to favour no significant circulating or post-prandial level changes for this hormone, indicating that bypassing the stomach may not directly alter ghrelin release.

The results for restrictive operations (Table 2) however revealed that of 22 studies, 50% reported an increase, 32% reported no significant change and only 18% reported a decrease. From clinical experience these operations are considered to decrease hunger and

Table 1
Modulation of Ghrelin after bypass procedures.

Author	Year	Procedure	No.	F/U	Ghrelin
Cummings et al. [36]	2002	RYGB	5	9–31 months	Decrease 24 h Ghrelin
Holdstock et al. [40]	2003	RYGB	10	12 months	Increase
Leonetti et al. [41]	2003	RYGB	11	9–15 months	NC (post-prandial)
Faraj et al. [42]	2003	RYGB	50	9–21 months	Increase with active weight loss
Tritos et al. [43]	2003	RYGB	6	10–26 months	Decrease (after glucose load)
Adami et al. [44]	2003	BPD	15	2 months	NC
Lin et al. [45]	2004	RYGB	34	10 min	Decrease immediately after surgery
Vendrell et al. [46]	2004	RYGB	34	6 months	Increase
Frühbeck et al. [47]	2004	RYGB	15	24 h	Decrease
Frühbeck et al. [48]	2004	RYGB	6	6 months	Decrease (compared to BPD and GB)
Frühbeck et al. [48]	2004	BPD	3	4 months	Not decreased to same extent as RYGBP
Frühbeck et al. [49]	2004	RYGP	8	6 months	Decrease
Adami et al. [50]	2004	BPD	24	12 months	Increase
Stoeckli et al. [51]	2004	RYGB	5	24 months	NC
Morinigo et al. [52]	2004	RYGB	8	6 weeks	Decreased levels, although no significant post-prandial change
García-Unzueta et al. [53]	2005	BPD	30	12 months	Increase
Korner et al. [54]	2005	RYGB	12	30–40 months	NC (post-prandial)
Mingrone et al. [55]	2006	BPD	6	14 days	Increased levels (though still less than controls), decreased pulsatility
Korner et al. [56]	2006	RYGB	9	180 min	No significant change
Chan et al. [57]	2006	RYGB	6	10–26 months	Decrease (post-glucose test)
Kotidis et al. [58]	2006	BPD-DS	13	18 months	Decrease
Stratis et al. [59]	2006	BPD-RYGB	20	12 months	NC
Couce et al. [60]	2006	RYGB	49	6 months	NC
Santoro et al. [61]	2006	DAIR	55	12–34 months	Decrease
Santoro et al. [62]	2006	DAIR	100	1–29 months	Decrease
Kotidis et al. [63]	2006	BPD-DS	13	18 months	Decrease
le Roux et al. [22]	2006	RYGB	6	6–36 months	NC (post-prandial)
Valera Mora et al. [64]	2007	BPD	11	18 months	Increase
Sundbom et al. [65]	2007	RYGB	15	12 months	Increase
le Roux et al. [23]	2007	RYGB	16	42 days	NC (post-prandial)
Whitson et al. [66]	2007	RYGB	10	6 months	NC
Liou et al. [67]	2008	Mini-RYGB	68	12 months	NC
Santoro et al. [68]	2008	DAIR	228	12–60 months	Decrease
Rodieux et al. [69]	2008	RYGB	8	9–48 months	Decrease (post-prandial)
Foschi et al. [70]	2008	RYGB	10	20% decrease BMI	Decrease, although no significant post-prandial change
Karamanakos et al. [71]	2008	RYGB+SG	16	12 months	Decrease
Heap et al. [72]	2008	Heap Procedure	246	2 months	Decrease
Garcia-Fuentes et al. [73]	2008	BPD	38	7 months	NC
Garcia-Fuentes et al. [73]	2008	RYGB	13	7 months	Increase
García de la Torre et al. [74]	2008	BPD	11	9 – 12 months	Decrease
García de la Torre et al. [74]	2008	RYGB	17	9 – 12 months	Decrease
Pardina et al. [75]	2009	RYGB	34	12 months	Increase

Levels are stated as basal unless indicated as post-prandial in brackets. NC = no significant change. RYGB – Roux-en-Y Gastric Bypass, BPD = Biliopancreatic Diversion, BPD-DS = Biliopancreatic Diversion with Duodenal Switch, GB = Gastric Band, VBG = Vertical Banded Gastroplasty, SG = Sleeve Gastrectomy, DAIR = Digestive Adaptation with Intestinal Reserve.

Table 2
Modulation of Ghrelin after restrictive surgery.

Author	Year	Procedure	No.	F/U	Ghrelin
Leonetti et al. [41]	2003	GB	10	9–15 months	NC (post-prandial)
Geloneze et al. [79]	2003	VBG	28	12 months	NC (post-prandial)
Hanusch-Enserer et al. [80]	2003	GB	12	12 months	NC (Basal)
Lin et al. [45]	2004	VBG	4	10 min	NC (Basal)
Frühbeck et al. [47]	2004	GB	12	24 h	Increase
Frühbeck et al. [48]	2004	GB	7	7 months	Not decreased to same extent as RYGBP
Frühbeck et al. [49]	2004	GB	8	6 months	Increase
Hanusch-Enserer et al. [77]	2004	GB	18	12 months	Increase at 12 months (not 6 months)
Nijhuis et al. [81]	2004	VBG	7	24 months	Increase
Nijhuis et al. [81]	2004	GB	10	24 months	Increase
Schindler et al. [82]	2004	GB	23	6 months	Increase
Stoeckli et al. [51]	2004	GB	8	24 months	Increase
Foschi et al. [83]	2005	VBG	12	20% decrease BMI	Increase, recovers response to meal
Korner et al. [56]	2006	GB	9	180 min	Decrease – significantly blunted (post-prandial)
Kotidis et al. [63]	2006	VBG	13	18 months	Increase
le Roux et al. [22]	2006	GB	6	6–36 months	NC (post-prandial)
Cigaina and Hirschberg [84]	2007	G-Pace	11	6 months	Increase of basal and post-prandial levels after activation
Shak et al. [85]	2008	GB	24	6–12 moths	NC
Foschi et al. [70]	2008	VBG	12	20% decrease BMI	Increase, decrease (post-prandial)
Wang et al. [86]	2008	GB	15	24 months	Increase (basal)
Wang et al. [86]	2008	SG	10	24 months	Decrease (basal)
García de la Torre et al. [74]	2008	VBG	17	9–12 months	NC

Levels are stated as basal unless indicated as post-prandial in brackets. NC = no significant change. GB = Gastric Band, VBG = Vertical Banded Gastroplasty, G-Pace = Gastric Pacing.

not necessarily satiety [76], and therefore the reported increase in ghrelin might be a reflection of a 'normalized' level of ghrelin lost in the morbidly obese. One study indeed reported no change of ghrelin levels at 6 months but an increase at 12 months [77], whilst another revealed a significantly blunted post-prandial response [56]. The modulation of ghrelin by these restrictive operations may not therefore necessarily contribute to the weight loss seen in these procedures, but rather may contribute to other physiological systems, including the successful long-term diabetic control seen in some gastric band patients [78]. It is also interesting to note that one of the two studies reporting a post-surgical increase in ghrelin was for the more recent sleeve gastrectomy procedure. This procedure requires increased study before further insights can be revealed regarding its gut hormonal modulation.

6.2. Gastrin

Gastrin is a peptide hormone produced by G cells in the duodenum and the pyloric antrum of the stomach by post-translational processing of preprogastrin. It stimulates acid secretion primarily by releasing histamine from enterochromaffin-like cells, and mediates many of its effects primarily through the CCK-2 receptor [87]. It was the first gut hormone to be studied in the context of bariatric surgery as early as 1975 following earlier studies that demonstrated a significant rise in this hormone after small bowel resection [29,30]. Although a minority of studies reveal an increase in basal and post-prandial levels mainly in jejuno-ileal bypass [88,89], the vast majority of bypass procedures reveal either no significant change or a decrease of both circulating and post-prandial levels [29,30,65,89–104]. The one study of gastric banding and gastrin reveals no significant post-operative change [85], whereas restriction by VBG has been shown to increase both basal and post-prandial levels [93,105]. Such a rise in gastrin might contribute to the rare complication of gastric pouch ulcer seen after VBG [106].

6.3. Glucose-dependent insulinotropic peptide or Gastric Inhibitory Peptide

Glucose-dependent insulinotropic peptide or Gastric Inhibitory Peptide (GIP) is 42 amino acids long, derived from a 153 amino acid precursor. It is released by K cells in the duodenum and proximal jejunum following carbohydrate and fat ingestion, where rate of absorption and not luminal content presides as the main stimulus for release [107].

GIP regulates adipocyte metabolism, though its effects on lipolysis and lipoprotein lipase activity, fatty acid synthesis and insulin-stimulated incorporation fatty acids to triglyceride maturation [108]. It promotes an energy storage state, and GIP-knockout mouse demonstrate a decreased adipocyte mass and a resistance to diet induced obesity. Although the effects on food intake are not clear, GIP does demonstrate an increase in energy expenditure [109]. It is known to have an incretin (or insulin-like) effect, and induces β-cell proliferation and inhibition of apoptosis [110].

Out of 10 foregut bypass studies, 1 revealed an increase in GIP [111], one reported no significant change [66], and 8 reported both basal and post-prandial decreases [94,112–118]. As the foregut is bypassed, a trend of decreased post-operative GIP levels can be discerned. As these operations are well known to improve type 2 diabetes control, the decreased incretin effect is unlikely to have a significant role in post-surgical diabetes resolution. The midgut bypass procedures follow a trend of the foregut bypass procedures, with the majority revealing decreased levels [92,119–124]. No clear trends can be discerned from the few studies on restriction [56,85,125,126].

6.4. Pancreatic Polypeptide

Pancreatic Polypeptide (PP) is a 36 amino acid peptide that is released mainly from cells at pancreatic islet peripheries according to an underlying circadian rhythm. It is known to relax the gallbladder, inhibit pancreatic secretion and regulate appetite. Its release is proportional to caloric intake and levels remain high for up to 6 h after a meal [127].

It mediates food intake via both the brainstem and the ARC in the hypothalamus, where it demonstrates a great affinity for the Y_4 receptor [128]. Injection into wild and genetically obese mice revealed long lasting effects on reduced food intake, decreased weight and improved glucose and lipid profile. Furthermore genetic expression to supraphysiologic levels also decreased food intake, alluding to its continuing anorectic effect despite chronic exposure [129].

Bariatric surgery does not appear to directly influence PP levels. Out of 8 bypass studies [22,65,92,94,95,130–132], all but one revealed no significant changes in basal or post-prandial PP levels. Similarly, of the 4 restriction studies [22,125,126,133], only one revealed a potential post-operative decrease [125]. Of these restrictive studies, only one

has been on gastric banding [22]. Research on the anorectic effects of PP is still ongoing, and further studies are required to elucidate the role of this peptide with some of the newer bariatric operations.

6.5. Cholecystokinin

Cholecystokinin (CCK) previously known as Pancreozymin was the first gut hormone to be studied in the context of appetite. It is derived from a 115 amino acid precursor, and secreted from I cells in the duodenum and jejunum after the ingestion of a meal. It has well characterized effects on gallbladder motility and both gastrointestinal motility and secretion. These actions occur largely via the CCK-1 (previously CCK-A) receptor and to a lesser extent the CCK-2 (previously CCK-B) receptor [134].

Peripheral injection of CCK in rodents inhibits food intake in a dose dependent manner, whereas CCK-knockout subjects and those receiving antagonists to the CCK-1 receptor diminish CCK's anorexigenic effect. However CCK-knockouts have the same weight as wild-type subjects [135], and tolerance develops to the presence of a continuous infusion. It has therefore been proposed that CCKs effects on appetite are considered 'physiological' as opposed to 'pharmacological'.

Only six studies of both bypass and restriction measured CCK, one of which is based on the newer bariatric procedure of gastric pacing [136]. There is however no clear trend amongst the other studies, with two revealing no significant change [114,137] and the same group reporting both increases[138, 139] and decreases in this hormone [140]. It is unlikely that bariatric surgery mediates is appetite effects via CCK.

6.6. Motilin

Motilin is a 22 amino acid peptide known for its eponymous effects on gastric and gut motility. It is a related peptide to ghrelin, and is released from epithelial cells of the upper intestine to act on its own receptor (motilin receptor) in association with Phase III of the migrating motor complex (MMC). Phase III activity has been proposed to contribute to development of hunger [141]. At lower concentrations it preferentially stimulates neuronal firing in the proximal gut and higher concentrations result in direct muscle contractions. The prokinetic antibiotic Erythromycin is a non-peptide agonist for the motilin receptor, however our understanding of its central nervous functional are limited as there is a lack of active motilin in rodent species. There is only limited data as to the presence of motilin mRNA in the brains of higher mammals [142]. Only three studies of both bypass and restriction measure motilin, where levels are found to both rise and decrease after bypass procedures [121,130,139].

6.7. Enteroglucagon

Enteroglucagon (EG) is an umbrella term referring to gut glucagon-like peptides that cross reacts with N-terminally directed antiglucagon antisera but not with C-terminally directed antisera. Two such peptides have been demonstrated in lower small intestine: glicentin (69 amino acids) and oxyntomodulin (37 amino acids). Both are products of the pre-proglucagon gene and are released post-prandially [143].

Of the two, Oxyntomodulin has proved to demonstrate stronger effects on appetite. Its actions inhibit gastric acid secretion and both central and peripheral injection leads to decreased food intake. It binds the GLP-1 receptor, and its anorectic effects are abolished in GLP-1 receptor knockout mice and by the GLP-1 antagonist exendin 9-39 [144]. Nevertheless, chronic administration decreases food intake, and also promotes energy expenditure [145].

Studies of gastric banding [22] and VBG [137] reveal no significant changes in this peptide, although ileal interposition in rat model has been shown to increase the gene expression of proglucagon [146]. Half of foregut bypass procedures, and all the midgut bypass procedures demonstrated an increase in enteroglucagon expression [22,121,132,137,147–149].

7. Midgut hormone

7.1. Neurotensin

Neurotensin (NT) is a 13 amino acid gut peptide [150] and neurotransmitter that is found in many parts of the brain, where cell bodies containing NT closely interact with the mesolimbic, mesocortical and nigro-striatal dopamine (DA) circuits [151]. It has been demonstrated to reduce food intake, and its expression is down-regulated in leptin deficiency (ob/ob mice) [152].

Five out of six bypass studies [121,139,140,149,153,154] reveal that NT is significantly increased after surgery, with one VBG study [155] revealing a decrease and one gastric band study [154] revealing an increase. A consistent increase in NT could contribute to some of the appetite effects of the bypass operations.

8. Hindgut hormones

8.1. Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is both a gut hormone and a neuropeptide produced by the post-translational processing of the pre-proglucagon gene. It is co-secreted by the L cells of the gastrointestinal tract with PYY and Oxyntomodulin. It is cleaved as a 36 or 37 amino acid peptide and gains further biological activity by truncation at the N-terminal [156]. Plasma levels increase rapidly after a meal, although its circulating half-life is less than 5 min. This occurs as due to its renal clearance and also from its degradation by circulating enzymes such as dipeptidyl peptidase IV (DPP-IV) [157].

GLP-1 suppresses gastric acid secretion and can acutely decrease food intake in rats (central injection) [158] and humans by increasing satiety and reducing hunger [159]. Along with peptide YY (PYY), it is considered to act as an "ileal-brake" where following ingestion of food, the distal gastrointestinal tract (hindgut) messages to the proximal gastrointestinal tract (foregut) to delay gastric and upper intestinal motility [160]. Five-day prandial injections of GLP-1 decreased body-weight in obese but otherwise healthy individuals by 0.55 kg [161], and the GLP-1 agonist exenatide also reduces food intake.

The central nervous effects of GLP-1 are diverse and include the behavioural responses to stress and anxiety [162]. Its effects on the reduction of food intake are considered to occur via two mechanisms. Firstly activation of GLP-1 Receptors in the hypothalamus regulate calorific intake and secondly GLP-1 Receptors in the Amygdala can induce malaise [163], a finding that may explain its role in conditioned taste aversion. Food intake suppression takes place through caudal brainstem circuits triggered by exogenous hindbrain GLP-1 Receptor activation via vagal signals [164]. In addition, endogenous GLP-1 Receptors located in nucleus tractus solitarius (NTS) neurons can also decrease food suppression and can be driven by gastric (but not duodenal) satiation signals [165].

GLP-1's effects on appetite can be abolished by vagotomy [166], although it has also been shown to play a role in lipolysis [167] and increasing energy expenditure through raised bodily temperature [168].

Although peripherally administered GLP-1 can also induce satiety, these effects may only partially occur through the peptide crossing the blood brain barrier [169]. This is because it has a short half-life (less than 2 min), which renders it unlikely to mediate all its effects through central pathways. The effects on the delay of gastric emptying have therefore been proposed as the most likely mechanism through which peripheral administration of GLP-1 regulates food intake [170].

GLP-1 acts through the GLP-1 receptor, a G-protein-coupled receptor of the family B subtype. These receptors are found in the

hypothalamus and the nucleus tractus solitarius (NTS). It has been reported to activate neurones at the ARC, the NTS and also the area postrema (AP) [171]. Interestingly central GLP-1 injection induces c-Fos expression in the PVN and not the ARC, and central injection of the GLP-1 antagonist exendin 9–39 to the ARC does not diminish the anorectic actions of peripheral GLP-1 [166], suggesting a dominant role for its effects in the brainstem. Both GLP-1 and its agonist are well known to induce nausea.

Of particular note are the powerful incretin effects of GLP-1, where it has been shown to significantly improve post-prandial glycaemic control. Its agonist exenatide has not yet been approved for the treatment of obesity, although it is now used in the treatment of Type 2 diabetes mellitus [172]. GLP-1 upregulates pancreatic β-cell genes, inhibits β-cell apoptosis and promotes β-cell neogenesis [173]. Although GLP-1 and GIP are both members of the glucagon peptide superfamily and share a close amino acid homology, they each work through their own distinct though structurally similar receptor [174].

Of the foregut bypass procedures (gastric bypass and biliopancreatic diversion), only one quoted a decrease of GLP-1 [175], two quoted no significant changes [114,115], but the vast majority of studies (86%) with a maximum follow-up of over 36 months revealed a rise of both basal and post-prandial GLP-1. Although there are only two studies of midgut bypass (jejuno-ileal bypass), both report an increased GLP-1, one with a follow-up of 20 years (Table 3).

In contrast, the three studies on restrictive surgery reveal two without any changes to GLP-1 after surgery, and the remaining study quoting an actual decrease in basal levels. The one study on gastric pacing also revealed a decreased post-procedural GLP-1.

These results reveal that such a rise in GLP-1 is likely to contribute to the post-operative decrease in food intake seen in bypass procedures, although the weight loss seen is not purely as a result of GLP-1 due to then finding that JIB patients increase the levels of this hormone, but do not demonstrate equivalent weight loss to the foregut bypasses (gastric bypass and biliopancreatic diversion).

Furthermore, the rise in GLP-1 can positively improve glycaemic control in type 2 diabetes. Controversy surrounds the small number of patients which have been diagnosed with nesidioblastosis, where islet β-cell neoproliferation can result in an adult-onset hyperinsulinaemic hypoglycaemia [176]. The exact contribution of GLP-1 on the development of nesidioblastosis after gastric bypass requires further elucidation. The paucity of studies on restrictive procedures nevertheless fits in with the clinical finding that they are not as temporally successful as bypass operations in correcting diabetes [177].

8.2. Peptide YY

Peptide YY (PYY) is a 36 amino acid peptide that is released in proportion to caloric intake from L cells primarily in the terminal ileum, colon and rectum, and the proximal ileum to a lesser extent

Table 3
Modulation of GLP-1 and PYY after bariatric surgery.

Author	Year	Procedure	No.	F/U	GLP-1	PYY
Naslund et al. [139]	1997	JIB	7	6–12 months	Increase (Basal and post-prandial)	Increase (Basal and post-prandial)
Naslund et al. [123]	1998	JIB	12	9 months–20 years	Increase (Basal and post-prandial)	
Alvarez Bartolomé et al. [186]	2002	VBG	12	12 months		Increased (post-prandial) compared to pre-operative levels
Cigaina and Hirschberg [136]	2003	G-Pace	11	6 months	Decrease	
Rubino et al. [114]	2004	RYGB	10	3 weeks	NC	
Lugari et al. [187]	2004	BPD	22	50% excess weight reduction	Increase (post-prandial)	
Clements et al. [115]	2004	RYGB	20	3 months	NC (basal)	
Korner et al. [54]	2005	RYGB	12	30–40 months	Increase (post-prandial)	
Valverde et al. [9]	2005	VBG	12	6 months	NC (basal), NC (post-prandial)	
Valverde et al. [188]	2005	BPD	19	6 months	Increase (Basal and post-prandial)	
Morinigo et al. [189]	2006	RYGB	9	6 weeks	Increase (post-prandial)	Increase (post-prandial)
Morinigo et al. [189]	2006	RYGB	34	12 months	Increase (post-prandial), although not for established type II diabetics	
Borg et al. [190]	2006	RYGB	6	6 months	Increase (post-prandial)	
Guidone et al. [116]	2006	BPD	10	1–4 weeks	Increase	
Korner et al. [56]	2006	GB	9	180 min		NC
Korner et al. [56]	2006	RYGB	9	180 min		Increase (post-prandial)
Chan et al. [57]	2006	RYGB	6	10–26 months		Increase (post-glucose test)
Stratis et al. [59]	2006	BPD-RYGBP	20	12 months		Increase
Santoro et al. [61]	2006	DAIR	55	12–34 months	Increase	Increase
le Roux et al. [22]	2006	GB	6	6–36 months		No significant change (post-prandial)
le Roux et al. [22]	2006	RYGB	6	6–36 months		Increase (post-prandial)
le Roux et al. [23]	2007	RYGB	16	42 days	Increase (post-prandial)	Increase (post-prandial)
Laferrere et al. [117]	2007	RYGB	8	1 month	Increase in response to oral glucose	
Whitson et al. [66]	2007	RYGB	10	6 months	Increase (basal) only in non-diabetics	
Reinehr et al. [175]	2007	GB	11	24 months	Decrease (basal)	Increase (basal)
Reinehr et al. [175]	2007	RYGB	19	24 months	Decrease (basal)	Increase (basal)
Korner et al. [191]	2007	GB	10	180 min	NC (post-prandial)	
Korner et al. [191]	2007	RYGB	13	180 min	Increase (post-prandial)	
Laferrere et al. [111]	2008	RYGB	9	1 month	Increase (after oral glucose)	
Shak et al. [85]	2008	GB	24	6–12 moths	NC	
Santoro et al. [68]	2008	DAIR	228	12–60 months	Increase	Increase
Rodieux et al. [69]	2008	RYGB	8	9–48 months	Increase (post-prandial)	Increase (post-prandial)
Karamanakos et al. [71]	2008	RYGB+SG	16	12 months		Increase
Heap et al. [72]	2008	Heap Procedure	246	2 months	Increase (post-prandial)	Increase (post-prandial)
Garcia-Fuentes et al. [73]	2008	BPD	38	7 months		Increase
Garcia-Fuentes et al. [73]	2008	RYGB	13	7 months		Increase
Salinari et al. [118]	2008	BPD	9	1 month	Increase (post-glucose test)	
Vidal et al. [192]	2008	RYGB	24	>36 months	Increase (post-prandial)	
de Carvalho et al. [193]	2009	RYGB	19	9 months	Increase (post-glucose test)	

Levels are stated as basal unless indicated as post-prandial in brackets. NC = no significant change. RYGB – Roux-en-Y Gastric Bypass, BPD = Biliopancreatic Diversion, GB = Gastric Band, VBG = Vertical Banded Gastroplasty, SG = Sleeve Gastrectomy, DAIR = Digestive Adaptation with Intestinal Reserve, G-Pace = Gastric Pacing.

[178]. PYY's functions include delayed gastric emptying and reduced gastric secretion. It is considered to contribute to the 'ileal-brake' phenomenon [160]. Following release, dipeptidyl peptidase IV (DPP-IV) cleaves the peptide at the N-terminal into two biologically active forms. PYY(1–36) corresponds to approximately 60% of circulating levels and PYY(3–36) for the remaining 40% of circulating PYY [179].

Peripheral injections decreases food intake in humans[180] and a variety of other mammals [181], and this can also be demonstrated by a central injection into the ARC. Interestingly however, injection into the CNS conversely results in an orexigenic effect. The anorectic effects are thought to occur through the Y_2 receptor [182] which is highly expressed on NPY neurones at the ARC, whereas the orexigenic effects are considered to be mediated through Y_1 and Y_5 receptors [183]. These results have led to some controversy in the literature, and it has been proposed that under physiological conditions, PYY does not typically reach Y_1 and Y_5 receptors to achieve a hunger effect, and typically results in decreased food intake. Furthermore, as the Y_2 receptor is also expressed in the NTS, and the nodose ganglion of the vagus nerve, a role for its activity via the vagus has been proposed [184]. This is substantiated by the abolishing of PYY food suppression by vagotomy [166].

The results of surgery on PYY closely reflect those seen for GLP-1 (Table 3). Here all the studies of bypasses (both foregut and midgut) quote increases in post-prandial and basal PYY levels. There were no decreases and no non-significant rises. These bypass procedures are stimulating the hindgut and activating the 'ileal brake'. Lugari et al. demonstrated that not only are PYY levels raised, but the levels of its breakdown enzyme (Dipeptidyl peptidase-4 – DPP-IV) are unchanged. The role of PYY however is still incompletely understood, and many studies fail to specify if levels achieve those of lean controls. Furthermore the finding that biliopancreatic diversion results in a greater increase in PYY and a lower weight loss than gastric bypass is also interesting as it might elude to other mechanisms that modulate PYY release. One mechanism for this could be the altered flow of bile, as Welch et al. performed a two armed study in Pavlov pouch canines undergoing either gastric bypass or a non-bariatric duodenal switch. They revealed that the surgical alteration of bile flow led to a greater rise in both basal and post-prandial PYY levels when compared to gastric bypass [185].

Of the three studies that measured PYY after restrictive surgery, two reported no significant changes, whereas one reported an increase.

9. Other hormones and animal models

A number of other hormones have been measured before and after bariatric operations, although they occur in such few studies that it becomes difficult to observe any trends as how metabolic surgery can modulate them. A few notable exceptions are mentioned below.

Vasoactive intestinal peptide (VIP), Serotonin (5HT) and Neuropeptide Y (NPY) are all gut and brain hormones. VIP increases gastrointestinal secretion and smooth muscle relaxation to augment intestinal motility, whereas Serotonin reduces appetite whilst NPY increases food intake. VIP was increased in one gastric bypass study after a glucose test [153], although further studies in both restriction and bypass revealed no significant effects of surgery [137]. Neither 5HT [137] or NPY [66,114] are modulated by bariatric operations in the reports to-date.

Of the six animal experiments studying gut hormones, five were in rodents (one restrictive [194] and four bypass procedures ([22,124,195,196]). Borg et al. not only demonstrated a rise in PYY and GLP-1 but also revealed up regulation of GLP-2 after BPD [196].

There is also recent evidence suggesting that a gastrointestinal peptide not historically considered a hormone, apolipoprotein AIV (Apo A-IV) can promote satiety. It is an approximately 46-kDa glycoprotein released from the small intestine, liver and hypothalamus in response to ingested triglyceride signals [197,198]. Apo A-IV first enters the intestinal lymph in chylomicrons or in lipoprotein-free form before entering the systemic circulation. Both systemic and central nervous administration result in a decreased meal size in rodents, while administration of Apo A-IV antiserum increases meal size [199]. Additionally Apo A-IV inhibits gastric emptying and carries both anti-inflammatory and anti-atherogenic properties.

Few studies have examined the post-bariatric changes of Apo A-IV, one demonstrates a 47% decrease at 1 month which normalises by one year [75], whilst another reports an increase at approximately 19 months after gastric bypass [200]. Although the mechanism for this is still unclear, it is interesting to note that PYY (typically increased after gastric bypass) can mediate intestinal Apo A-IV release [201], whilst Apo A-IV can work in association with the CCK(1) Receptor to modulate the PYY activation of vagal afferents and also decrease gastric emptying [202].

10. Conclusions

Gut peptides may be a major contributor through which the gastrointestinal tract can communicate with the brain to regulate feeding behaviour and energy balance. This gut-brain axis has developed a sophisticated collection of peptides with which to relay its messages. These can travel directly via the nervous system, the systemic circulation or both to deploy energetic information to the brainstem and higher food regulatory centres. Bariatric or Metabolic surgical procedures are not all the same and each transmits a characteristic hormonal profile that reaches the brain. Anatomical variations in surgery can result in distinct metabolic message that ultimately leads to an improvement in both obesity and metabolic status. Although 34 years of surgical gut hormonal modulation research has existed, the field continues to grow and requires continued efforts to build on current knowledge.

So far, operations that bypass the foregut (RYGB and BPD) demonstrate a much stronger gut hormone responses than purely restrictive procedures such as gastric banding. These enhanced actions have a proven benefit in terms of weight loss and also metabolic outcomes, including a significant improvement in the resolution of diabetes [27]. Consequently, procedural decision-making is now guided by choosing operations that specifically improve the individual metabolic dysfunction in each patient. Novel operative variations and improved technique should aim to further enhance current gut hormonal effects, but also introduce the modulation of other gut hormonal pathways. These can add to the metabolic surgical arsenal in such a way that can ultimately combat each patient's metabolic dysfunction with a 'tailor-made' operation, whilst also revealing further mechanistic knowledge of operative success.

As a result, the study of these operations offers us unique insights of how modified gut hormonal release can provide new treatments and targets for obesity, appetite and metabolic disorders.

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