Mechanisms of Weight Loss after Gastric Bypass and Gastric Banding

Marco Bueter   Hutan Ashrafian   Carel W. le Roux

Department of Investigative Medicine, Hammersmith Hospital, Imperial College London, UK

Summary
The obesity epidemic is a major health problem that is associated with increased morbidity and mortality. Gastrointestinal hormones have been increasingly understood to be an important element in appetite regulation. Several gastrointestinal hormones can contribute to obesity by modulating the activity of the gut-brain axis. Bariatric surgery is currently the most effective therapy for significant and sustained weight loss in morbidly obese patients. Understanding how gut hormones are altered by bariatric procedures has contributed to our understanding of the mechanisms of appetite. In this review, we address several gastrointestinal hormones that are associated with obesity and consider how their levels are altered after bariatric surgery. The review also addresses specific effects of different gut hormones on appetite, hunger, and energy balance.

Introduction

The personal, social, and economic consequences of the obesity epidemic can be devastating [1–3]. Major research efforts are being directed towards the development of successful weight loss therapies. Consequently, the neuroendocrine regulation of food intake and weight gain has been increasingly studied. This is especially the case for gut hormones that may have future pharmacotherapeutic applications [4–6]. At this stage, the available anti-obesity drugs are moderately effective at achieving weight loss, whilst their side-effects remain problematic. The most effective therapeutic option currently available to obtain significant and sustained weight loss is bar-

iatric surgery [7, 8]. The exact mechanisms involved in weight loss after these surgical techniques are not completely understood, but a number of studies have demonstrated that alterations in circulating gut hormone levels may play an important role [9–11]. There is a growing body of evidence suggesting that gut hormones may be involved in transmitting information from the gastrointestinal tract to the appetite centres in the central nervous system (CNS) as part of the gut-brain axis. Alterations in these hormones after bariatric procedures may partly explain the mechanisms by which surgery reduces appetite and induces sustained weight loss.

Basic Principles of Common Bariatric Procedures

Bariatric procedures are surgical procedures performed to treat obesity through modification of the gastrointestinal tract. Surgical procedures for the removal of body fat such as liposuction or abdominoplasty are not considered as bariatric surgical procedures as their weight loss is small and unsustained. The National Institute of Clinical Excellence (NICE) criteria for bariatric surgery recommends patients to be eligible for surgical procedures if they have a BMI ≥ 35 kg/m^2 with an obesity-related comorbidity or patients with a BMI ≥ 40 kg/m^2. Patients need to have an instituted but failed adequate exercise and diet programme (with or without adjunctive drug therapy). There are two main categories of surgical procedures: restrictive procedures like gastric banding (fig. 1) and bypass procedures like Roux-en-Y gastric bypass (fig. 2). Restrictive surgery aims to prevent excessive food consumption by reducing the volume of the stomach and reducing appetite [12]. At present, the Roux-en-Y gastric bypass procedure is widely accepted to be the gold standard of bariatric surgery [13, 14]. Here, a small stomach pouch is created and connected to the distal small intestine. The upper part of the small intestine is then reattached in a Y-shaped configuration (fig. 2).

Generally, gastric banding results in a weight loss of approximately 20%, whilst the Roux-en-Y gastric bypass results
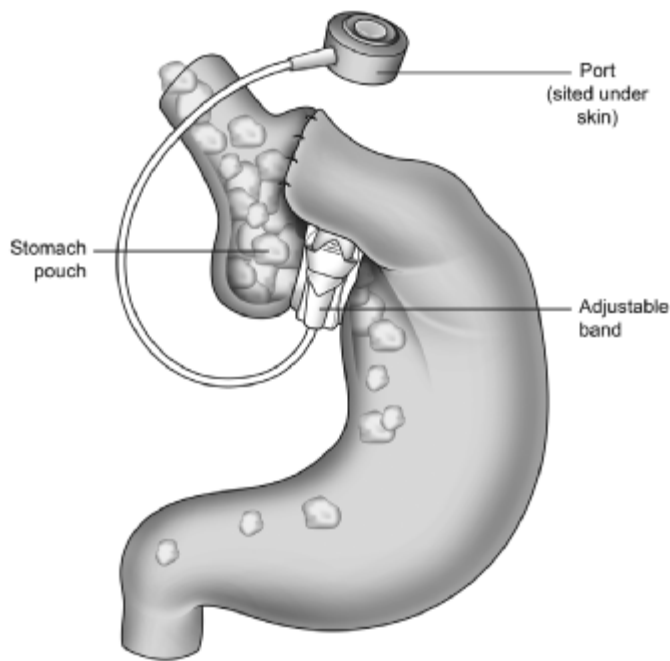
Dr. Carel W. le Roux, MBChB, Ph.D., MRCP, MRCPath
Department of Investigative Medicine
Hammersmith Hospital, Imperial College London
Du Cane Road, London, W12 0NN, UK
Tel. +44 20 83833242
c.leroux@imperial.ac.uk

Fig. 1. Gastric banding (pouch size: 10–20 ml).

Fig. 2. Roux-en-Y gastric bypass (pouch size: 10–20 ml).

in approximately 25% weight loss [15]. Overall, the bypass procedures induce greater weight loss than restrictive procedures [8] and are characterised by an immediate and prolonged loss of appetite. Furthermore, weight loss after bypass-type procedures results from reduced appetite and calorie intake rather than malabsorption [16]. Several studies report a dramatic improvement of obesity-related comorbidities and a significant decrease in mortality after bariatric surgery [7, 8, 17]. Surgery is still associated with risks and adverse effects after gastric bypass. These include dumping syndrome in about 20% of patients, anastomotic leakage (1–2%), incisional hernia (7%), infections (6%), deep vein thrombosis (1–3%) [18], pulmonary embolism (2%) [19], and pneumonia (4%) [20]. To reduce the incidence of complications, patients should be treated in high-volume centres with clinicians experienced in bariatric surgery [21].

Appetite Regulation via the Gut-Brain Axis

The hypothalamus as part of the central melanocortin system plays a crucial role in the regulation of food intake. Several hypothalamic nuclei have been identified, all of which are interconnected by energy homoeostasis-regulating circuits [22]. Among these, the arcuate nucleus (ARC) acts as an important relay centre. The ARC can be functionally divided into a medial and a lateral part. Both parts integrate and distribute peripheral information from hormonal and neural signals that reflect metabolic status of the periphery to the brain [23, 24]. Neurons within the medial ARC co-express neuropeptide Y (NPY) and agouti-related peptide, which stimulates
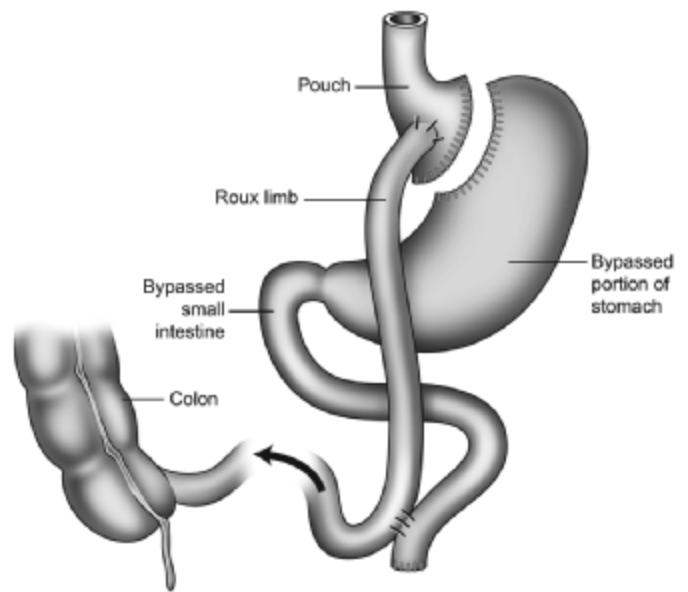
food intake and weight gain by increasing appetite [24]. The neurons in the lateral ARC co-express pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript, which both promote weight loss by decreasing appetite [23]. Furthermore, NPY can also suppress appetite and is a selective ligand for the Y4 receptor subtype which is expressed at the area postrema (AP) and the other appetite-regulating areas of the melanocortin pathway [25, 26]. The balance between the activities of NPY-POMC neuronal circuits is critical for the maintenance of body weight [23, 24, 27]. Due to its immediate vicinity to brain regions with an incomplete blood-brain area, the ARC and the brainstem are ideally located to receive incoming signals from the periphery [24]. Humoral signals from the periphery may be well delivered by gut hormones crossing the blood-brain barrier through the circumventricular organs after being released into the circulation. Sensory input to the CNS is also forwarded by vagal and somatosensory afferent fibres in the gastrointestinal tract all ending centrally in the nucleus tractus solitarius (NTS) within the brainstem.

Information about energy stores and recent food intake is mutually exchanged between the hypothalamus and brainstem, influencing the perception of satiety [24]. When communication with higher brain centres is surgically interrupted, these brain centres can still respond independently to peripheral signals [28].

Gastrointestinal Hormones

The gut-brain axis is a major component of appetite regulation. Gastrointestinal hormones have either an orexigenic or anorexigenic action on food intake, and their levels are altered

Table 1. Origin, effects, and altered levels of gastrointestinal hormones after bariatric surgery

Gastrointestinal hormones	Origin	Behavioral brain effects		Other effects	Alterations after surgery	
		hunger	satiety		gastric bypass	gastric banding
Ghrelin	stomach	↑	↓	unknown	unclear	unclear
Glucagon-like peptide-1	ileum (L-cell)	↓	unknown	insulin secretion ↑ β-cell proliferation ↑ β-cell gene expression ↑ gastric acid secretion ↓ gastric emptying ↓ apoptosis ↓	↑	no change
Peptide YY	ileum (L-cell)	↓	↑	gastric acid secretion ↓ pancreatic and intestinal secretion ↓ gastrointestinal motility ↓	↑	no change
Gastric inhibitory polypeptide	duodenum and jejunum (K-cell)	unknown	unknown	fat deposition ↑ triglyceride accumulation ↑ insulin secretion ↑ β-cell proliferation ↑ apoptosis ↓ bone formation ↑	↓ (diabetics)	unknown
Cholecystokinin	duodenum and jejunum (I-cell)	↓	↑	gastric emptying ↓ pancreatic secretion ↑ gall bladder contraction ↑	no change	no change
Pancreatic polypeptide	pancreas	↓	unknown	gastric emptying ↓ leptin levels (white adipose tissue) ↓	no change	no change

after bariatric surgery [29]. The hormones that are reviewed include ghrelin, glucagon-like peptide-1 (GLP-1), peptide YY (PYY), gastric inhibitory polypeptide (GIP), cholecystokinin (CCK), and pancreatic polypeptide (PP). Table 1 summarises the origin and effects of the addressed hormones as well as their altered levels after gastric bypass and gastric banding surgery.

Ghrelin
Ghrelin is a 28-amino-acid gut peptide derived predominantly from the stomach [30]. So far, it is the only known orexigen (appetite-stimulating hormone). Ghrelin increases food intake in rodents [31] and humans [22] via the growth hormone secretagogue receptor (GSH-R). Most clinical studies have examined its potential for the treatment of conditions characterised by anorexia and cachexia [32–34]. Circulating ghrelin levels peak in the fasting state and decrease after food intake [35]. Plasma ghrelin levels seem to be primary regulated by the calorific intake [36], and it also stimulates appetite and food intake in obese individuals [37]. Ghrelin levels are lower in weight-stable obese individuals and rise after diet-induced weight loss [38]. The postprandial decrease in plasma ghrelin is absent or attenuated in the obese [39, 40].

Glucagon-Like Peptide-1
GLP-1 is a neuropeptide hormone which is produced by post-translational processing of the preproglucagon gene in the CNS and the gastrointestinal tract [41]. GLP-1 is secreted from intestinal endocrine L-cells that make direct contact with the gut lumen and is therefore believed to sense the arrival and passage of nutrients along the gastrointestinal tract [41]. The brainstem is an important site of action for peripheral GLP-1, and it has been demonstrated that both peripheral and central GLP-1 administration activates neurons in the ARC, the hypothalamic paraventricular nucleus, NTS, and AP, all increasing satiety and decreasing hunger [42, 43]. GLP-1 is released after food intake, but differences have been observed between normal weight and obese individuals [44–46]. GLP-1 is a potent incretin (insulin-stimulating peptide). GLP-1 administration causes gastrointestinal side-effects including decreased gastric acid secretion and delayed gastric emptying [47, 48]. Vagotomy can resolve the gastrointestinal effects of GLP-1, indicating an important role of the vagus nerve for mediating its anorectic effects [42].

The effects of GLP-1 in reducing appetite and calorie intake in humans have been shown to occur in a dose-dependent manner [49, 50]. Increased energy expenditure by raising body temperature [51, 52] and regulating lipogenesis [53, 54] have been suggested to be part of GLP-1's central actions, while some studies suggest its role in promoting lipolysis [54]. Subcutaneous GLP-1 treatment improves glycaemic control in patients with type 2 diabetes mellitus (T2DM) within 3 weeks [55], while the GLP-1 agonist exenatide improves HbA1c levels in the long term [56]. In addition, GLP-1 increases pancreatic β-cell gene expression, promotes β-cell proliferation, and inhibits apoptosis [57].

Peptide YY

PYY is a 36-amino-acid peptide and a member of the pancreatic polypeptide family [58]. PYY levels are highest in the colon and rectum and diminish to lower levels in the small intestine [59]. As is the case for GLP-1, PYY is stored and released from L-cells of the gastrointestinal tract [59, 60]. PYY is secreted in proportion to calories ingested and independent of gastric distension [59]. PYY inhibits gastric, pancreatic, and intestinal secretion as well as gastrointestinal motility [59, 61]. The major form of circulating PYY is the N-terminally truncated PYY3–36, which has high affinity for the Y2 receptor and a lesser affinity for Y1 and Y5 receptors [62]. Although initially controversial, peripheral administration of PYY3–36 at physiological doses has now been accepted to reduce food intake in rodents, primates, and humans in the short term [63–66]. PYY3–36 activates anorectic POMC-expressing neurons in the ARC, and direct intra-ARC administration of PYY3–36 reduces food intake in rats [67]. It has been demonstrated for both PYY and GLP-1 that ablation of the vagus-brainstem-hypothalamus pathway leads to a moderation of their anorectic effects [42]. Obese individuals are sensitive to the effects of PYY, as peripheral PYY administration in obesity reduces food intake to the same extent as in normal weight individuals, but circulating postprandial PYY levels are lower in the obese [68]. Hence, exogenous administration of PYY3–36 has attracted considerable interest as a possible therapeutic strategy [69]. Long-term augmentation of dietary protein induces an increase of plasma PYY levels in mice, leading to less food intake and reduced adiposity [70]. PYY3–36 administration in humans at levels above physiological ranges results in nausea [67, 68], although this does not occur within its physiological range [64]. Elevated fasting levels of PYY can also be found in gastrointestinal diseases associated with appetite loss, including inflammatory bowel disease (IBD), steatorrhea due to small intestinal mucosal atrophy, and chronic destructive pancreatitis [71].

Gastric Inhibitory Polypeptide

GIP is a 42-amino-acid peptide released from duodenal and jejunal K-cells after ingestion of nutrients [72]. GIP is also known as glucose-dependent insulinotropic polypeptide. GIP facilitates the dispersion of both glucose and fat [73] and aids fat deposition and triglyceride accumulation in adipocytes. The peptides exert several anabolic adipocyte actions as well as lipolytic effects [73, 74]. GIP receptor-deficient mice (GIPR–/–) have lower adipocyte mass and are completely resistant to diet-induced obesity [75]. GIP on its own has no acute impact on food intake [72], but acts in concert with GLP-1 to control food intake and energy absorption. Similar to GLP-1, GIP increases glucose-dependent insulin secretion, β-cell proliferation, and resistance to apoptosis [76]. GIP enhances bone formation via stimulation of osteoblast proliferation and inhibition of apoptosis. Its levels are raised in obesity [72].

Cholecystokinin

CCK was first shown to inhibit food intake nearly 30 years ago [77]. It is widely distributed within the gastrointestinal tract, but most CCK is synthesised in the duodenum and jejunum in response to the presence of nutrients [78]. CCK is an active peptide that is derived from numerous posttranslational modifications of pro-CCK. Several gastrointestinal functions are mediated by CCK, including the delaying of gastric emptying, the stimulation of pancreatic enzyme secretion, and gall bladder contraction [79, 80]. CCK is also involved in the regulation of food intake by acting via vagal afferents to induce satiety. Other neurotransmitters such as serotonin and noradrenaline may work in conjunction with CCK to coordinate gastrointestinal activity [81]. In healthy elderly people, high CCK and PYY levels are associated with delayed gastric emptying and reduced gallbladder contractility [82]. These high CCK and PYY levels facilitate long-lasting satiety and hunger suppression after meals and can lead to caloric restriction and malnutrition in the elderly [82].

Pancreatic Polypeptide

PP belongs to a family of peptides including NPY and PYY. PP is released from the pancreas in response to ingestion of food. Plasma PP has been shown to be reduced in conditions associated with increased food intake and elevated in anorexia nervosa [83]. Intravenously administered PP induces negative energy balance by decreasing food intake and gastric emptying while increasing energy expenditure. The mechanism of PP action involves modification of expression of feeding-regulatory peptides (decrease in orexigenic NPY, orexin, and ghrelin along with an increase in anorexigenic urocortin) and activity of the vagovagal or vagosympathetic reflex arc. PP reduces leptin in white adipose tissue and ACTH-releasing factor gene expression [84].

Gut Hormones and Appetite after Bariatric Surgery

Studies on gastrointestinal hormones after bariatric surgery can provide further information on the complex mechanisms of appetite regulation, satiety, and energy expenditure. Changes in appetite are reported within days following bariatric surgery [10]. Postprandial levels of gastrointestinal hormones that induce satiety, such as GLP-1 and PYY, are elevated after gastric bypass surgery [9], but not after gastric banding [29]. An optimally inflated gastric band reduces hunger and elevates satiety [12], but changes in appetite are independent of gut hormone alterations [29]. Furthermore, octreotide administration does not inhibit food intake in patients with gastric bands, indicating that gut hormone responses are absent [29]. Therefore, non-hormonal mechanisms have been suggested to reduce hunger following gastric banding [29]. In contrast, several studies have demonstrated that postprandial PYY and GLP-1 levels start rising as early as 2 days after gas-

tric bypass and remain elevated for many months after surgery [10, 11]. PYY and GLP-1 responses seem to correlate with different levels of weight loss: patients with 20% weight loss after gastric bypass operations show lower PYY and GLP-1 levels compared with patients that have lost 40% of their weight after surgery [10]. Moreover, appetite and food intake can be increased by administration of octreotide after gastric bypass, suggesting an inhibition of the satiety gastrointestinal hormone response [10]. The proposed mechanism behind these findings is that bariatric surgery stimulates the distal L-cells to secrete gastrointestinal hormones such as PYY and the enteroglucagon family of peptides [29]. As a result, patients have long-term decreased appetite after gastric bypass. The combination of gastrointestinal hormone responses might contribute to the successful weight loss and its maintenance after bariatric surgery, as the combined effect of exogenous elevation of PYY and GLP-1 reduces food intake more than predicted by individual hormone infusions alone [85].

In contrast, changes in ghrelin levels after bariatric surgery are more controversial. Cummings et al. [38] described markedly suppressed ghrelin levels after gastric bypass while diet-induced weight loss was associated with increased levels of plasma ghrelin. The suggestion was that reduced ghrelin contributes to the weight loss after gastric bypass [38], but conflicting results have been published [86–90]. Thus, the role of ghrelin after gastric bypass remains unclear. Ghrelin secretion might in fact be modified by other gastrointestinal hormones whose levels change in response to the altered gastrointestinal anatomy. However, since obesity is associated with lower levels of ghrelin, it seems unlikely that reducing the level of ghrelin would, by itself, induce weight loss [91].

Less is known about changes in GIP, CCK, and PP levels after bariatric surgery. While both CCK and PP levels seem to be unaltered following bariatric surgery [10, 92], GIP levels are significantly reduced in diabetic patients following bypass surgery [93]. However, no changes in GIP levels were found in non-diabetics [93].

Long-term follow-up data on the changes in gastrointestinal hormones after bariatric surgery are still awaited. Surgery modulates a number of gut hormones and probably allows them to act in concert in such a way as to affect appetite optimally. Understanding the contribution each hormone makes to appetite control within the setting of gastric bypass surgery may be the stepping stone to future anti-obesity treatments.

Conclusions

Gastric bypass surgery is associated with elevated satiety and satiety-inducing gut hormones. The satiety effects can be reversed by blocking the hormonal responses. Bariatric surgery is currently the only therapy inducing significant and sustained weight loss, but surgery carries the risk for serious complications. Thus, bariatric surgery may be used as a model to examine the physiological mechanisms of weight loss and to develop future surgical and non-surgical weight loss treatments.

Disclosure

The authors declared no conflict of interests.

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