Bariatric surgery as a model to study appetite control

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The obesity epidemic and its associated morbidity and mortality have led to major research efforts to identify mechanisms that regulate appetite. Gut hormones have recently been found to be an important element in appetite regulation as a result of the signals from the periphery to the brain. Candidate hormones include ghrelin, peptide YY, glucagon-like peptide-1 and gastric inhibitory polypeptide, all of which are currently being investigated as potential obesity treatments. Bariatric surgery is currently the most effective therapy for substantial and sustained weight loss. Understanding how levels of gut hormones are modulated by such procedures has greatly contributed to the comprehension of the underlying mechanisms of appetite and obesity. The present paper is a review of how appetite and levels of gastrointestinal hormones are altered after bariatric surgery. Basic principles of common bariatric procedures and potential mechanisms for appetite regulation by gut hormones are also addressed.

Bariatric surgery: Appetite control model: Gut hormones: Obesity

Abbreviations: ARC, arcuate nucleus; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; PYY, peptide YY.
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Bariatric surgery

Bariatric surgery, also known as weight-loss surgery, refers to the various surgical procedures performed to treat obesity by modifying the gastrointestinal tract in order to reduce nutrient intake and/or absorption. Procedures for surgical removal of body fat such as liposuction or abdominoplasty are not considered bariatric surgical procedures. Patients who have a BMI ≥ 35 kg/m² with an obesity-related comorbidity or patients with a BMI ≥ 40 kg/m² who have instituted an adequate exercise and diet programme (with or without adjunctive drug therapy) that has failed meet the National Institute of Clinical Excellence criteria for bariatric surgery(12). Surgical procedures can be grouped in two main categories: restrictive procedures, e.g. gastric banding (Fig. 1); bypass procedures, e.g. Roux-en-Y gastric bypass (Fig. 2). Restrictive surgery works by reducing the volume of the stomach and physically preventing excessive consumption of food(13). However, the most common form of bariatric surgery worldwide is Roux-en-Y gastric bypass surgery(14,15). Here, a small stomach pouch is created with a stapler

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device and connected to the distal small intestine. The upper part of the small intestine is then re-attached in a ‘Y’-shaped configuration (Fig. 2). In general, the bypass procedures lead to more weight loss than the restrictive procedures(8). Typically, gastric banding results in a weight loss of approximately 20%, whilst the Roux-en-Y gastric bypass results in approximately 30% weight loss(16). Weight loss after bypass-type procedures has been shown to be a result of energy intake rather than malabsorption(17). Several recent studies have reported a dramatic improvement in obesity-related comorbidities and a decrease in mortality after bariatric surgery(8,18,19). Adverse effects after gastric bypass include dumping syndrome in about 20% of patients, leaks at the surgical anastomosis (12%), incisional hernia (7%), infections (6%), deep-vein thrombosis (1–3%) (20), pulmonary embolism (2%) (21) and pneumonia (4%) (22). To reduce the incidence of complications, patients should be cared for in high-volume centres with clinicians experienced in bariatric surgery (23).

**Appetite regulation via the gut–brain axis**

The hypothalamus contains part of the central melanocortin system and plays a critical role in the regulation of food intake. It has a number of nuclei, including the arcuate nucleus (ARC), paraventricular nucleus, ventromedial nucleus and the dorsomedial nucleus, all of which are interconnected by circuits that regulate energy homeostasis(24). The ARC receives and acts on circulating appetite signals including the modulated release of several key amino acid neurotransmitters(25,26). The neurons in the medial ARC co-express neuropeptide Y and agouti-related peptide, which stimulate food intake and weight gain by increasing appetite(26). By contrast, the neurons in the lateral ARC co-express pro-opiomelanocortin (also known as corticotrophin–lipotropin) and cocaine-and-amphetamine-regulated transcript, which both promote weight loss by decreasing appetite(25). Both the ARC and the brainstem are ideally positioned to interact with circulating humoral factors and to receive signals from the periphery(26). Thus, gut hormones may act directly in the brain after being released into the circulation and entering through the circumventricular organs. Neuropeptide Y can suppress appetite and is a selective ligand for the Y4 receptor subtype, which is expressed at the area postrema and the other appetite-regulating areas of the melanocortin pathway(27,28). The balance between the activities of neuropeptide Y–pro-opiomelanocortin neuronal circuits is critical for the maintenance of body weight(25,26,29). After food is ingested sensory input to the central nervous system is forwarded by vagal and somatosensory afferent fibres in the gastrointestinal tract that all end in the nucleus tractus solitarius within the brainstem. Reciprocal pathways between the hypothalamus and brainstem pass on information about energy stores and recent food intake, influencing the perception of satiety (26). These brain centres can respond independently to peripheral signals when communication with higher brain centres is surgically interrupted(30). Peripheral feedback to the hypothalamus is complex. Many circulating signals, including gut hormones, can have direct access to the ARC(29). These neuronal interactions through central melanocortin pathways therefore reveal the critical role this system has in the regulation of hunger, satiety and energy expenditure(31). However, the homeostatic melanocortin system may protect against weight loss more robustly than it does against weight gain(32). In case of changes in body adiposity, the brain triggers physiological mechanisms that resist weight change through compensatory changes in appetite and metabolic rate(33,34).

**Gut hormones**

**Ghrelin**

Ghrelin is a twenty-eight-amino acid gut peptide derived predominantly from the stomach and pituitary gland(35). So
far, it is the only gut hormone with an orexigenic action. It acts via the growth hormone secretagogue receptor to increase food intake in rodents(36) and also stimulate food intake in human subjects(24). Clinical studies have thus concentrated on its use as an orexigenic agent in conditions characterized by anorexia and cachexia(37–39). Circulating ghrelin levels peak in the fasting state and fall after a meal(40). Energy intake seems to be the primary regulator of plasma ghrelin levels(41). Ghrelin stimulates appetite and food intake also in obese individuals(42). Ghrelin levels are lower in weight-stable obese individuals and rise after diet-induced weight loss(43). The postprandial decrease in plasma ghrelin is absent or attenuated in the obese, which suggests that ghrelin might be involved in the pathophysiology of obesity(44,45).

**Glucagon-like peptide-1**

Glucon-like peptide-1 (GLP-1) is a neuropeptide hormone produced by post-translational processing of the preproglucagon gene in the central nervous system and the gastrointestinal tract(46). Preproglucagon is secreted in the gastrointestinal tract by the endocrine L-cells that also secrete peptide YY (PYY)(46). The GLP-1 receptor belongs to the G-protein-coupled receptors(47). These receptors have been identified in neurons of the nucleus tractus solitarius, extending to regions of the hypothalamus that are important for the regulation of food intake(48). Peripheral as well as central GLP-1 administration activates neurons in the ARC, the hypothalamic paraventricular nucleus, the nucleus tractus solitarius and the area postrema, inducing increased satiety and decreased hunger(47,49). Usually, GLP-1 is released after energy intake, but differences have been observed between normal-weight and obese individuals(30–32). GLP-1 is a potent incretin. It also suppresses gastric acid secretion and delays gastric emptying(53,54). These effects can be resolved by vagotomy, indicating an important role of the vagus nerve in mediating the anorectic effects of GLP-1(50). Peripheral GLP-1 infusions have been found to cause a dose-dependent reduction in food intake, while administration of exenatide (an agonist of the GLP-1 receptor) markedly reduces food intake(55,56). Central actions of GLP-1 might also lead to increased energy expenditure by raising body temperature(57,58). GLP-1 has been shown to promote lipolysis(59,60), although some studies have suggested a role in lipogenesis(60). Glycaemic control in patients with type 2 diabetes mellitus improves after 3 weeks of treatment with subcutaneous GLP-1(61) while the agonist exenatide improves HbA1c in the long term(62). Furthermore, GLP-1 has been shown to up regulate the expression of pancreatic β-cell genes, promoting β-cell proliferation and inhibiting apoptosis(63). Exenatide enhances insulin secretion and suppresses glucagon release(64). In phase III clinical trials exenatide has been found to reduce body weight by 3–4 kg, although not all patients respond equally(66,67). Exenatide is not currently approved as an obesity treatment but has been approved for the treatment of type 2 diabetes mellitus. However, nausea is a common adverse effect of this treatment and this effect may relate to reduced gastric emptying or direct effects of the central nervous system(68).

**Peptide YY**

As a thirty-six-amino acid peptide PYY is a member of the pancreatic polypeptide family(69). It is found throughout the human small intestine, with highest levels in the colon and rectum(67). PYY is released after a meal from the endocrine L-cells of the gastrointestinal tract, where it is stored with GLP-1(67,68). PYY is secreted in proportion to the amount of energy ingested and is independent of gastric distension(67). PYY inhibits gastric, pancreatic and intestinal secretion as well as gastrointestinal motility(69,70). 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(71). Although initially controversial, peripheral administration of PYY3–36 at physiological doses has now been accepted to reduce food intake in rodents, primates and human subjects in the short term(72–75). PYY-knock-out mice are characterized by dysregulation of energy homeostasis(76). PYY3–36 activates anorectic pro-opiomelanocortin-expressing neurons in the ARC and direct intra-ARC administration of PYY3–36 reduces food intake in rats(77). Furthermore, it inhibits neuropeptide Y neurons, which might also contribute to its anorectic effects(78). These effects of PYY3–36 can be blocked by the administration of a specific Y2 antagonist. In addition, PYY3–36 does not reduce appetite in Y2-knock-out mice(77,79). Similar to GLP-1, ablation of the vagus–brain–hypothalamus pathway leads to a moderation of the anorectic effects, indicating a role of the vagus nerve in the neuronal messaging of PYY(49). Obese individuals are sensitive to the effects of PYY, as peripheral PYY administration in the obese reduces food intake to the same extent as in normal-weight individuals(80), but circulating postprandial PYY levels are lower in the obese(80). Exogenous administration of PYY3–36 has attracted considerable interest as a possible therapeutic strategy(81). Long-term augmentation of dietary protein induces an increase in plasma PYY levels in mice, leading to less food intake and reduced adiposity(82). PYY3–36 administration in human subjects to levels within the physiological range reduces food intake without causing nausea(77,80), whereas higher pharmacological doses can result in nausea(73). Sensations of hunger, satiety and nausea might all be points along the same physiological spectrum(83), and nausea is associated with all high-dose satiety-inducing gastrointestinal hormones, including cholecystokinin(83), oxyntomodulin(63) and GLP-1(85). Elevated fasting levels of PYY have also been observed in several gastrointestinal diseases associated with appetite loss, including inflammatory bowel disease, steatorrhoea as a result of small intestinal mucosal atrophy and chronic destructive pancreatitis(85). Furthermore, in healthy elderly individuals high cholecystokinin and PYY levels are associated with delayed gastric emptying and reduced gall-bladder contractility(86). These high cholecystokinin and PYY levels facilitate long-lasting satiety and hunger suppression after meals and can lead to restriction of energy intake and malnutrition in the elderly(86).

**Gastric inhibitory polypeptide**

Gastric inhibitory polypeptide (GIP) is a forty-two-amino acid incretin peptide, which is released from endocrine...
K-cells in the duodenum and proximal jejunum within minutes after food ingestion. The main stimulus for GIP secretion is the presence of glucose and fat. GIP promotes energy storage by direct actions on adipose tissue. The peptides exert several anabolic adipocyte actions as well as lipolytic effects. GIP-receptor-knock-out mice have lower adipocyte mass and display a resistance to diet-induced obesity. GIP on its own has no acute impact on food intake, 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. GIP levels have been found to be elevated in obese individuals.

Gut hormones and appetite after bariatric surgery

Changes in appetite are evident within days of bariatric surgery. Postprandial levels of gastrointestinal hormones that induce satiety, such as GLP-1 and PYY, are elevated after gastric bypass surgery, but not after gastric banding. It has been shown that hunger is reduced and satiety is elevated if gastric bands are optimally inflated. These changes in appetite appear independent of any gut hormone alterations. Administration of octreotide, which would inhibit gut hormone responses, does not affect food intake after gastric banding. Thus, non-hormonal mechanisms have been suggested. In contrast, studies have demonstrated that postprandial PYY and GLP-1 levels start rising as early as 2d after gastric bypass and can remain elevated for many months after surgery. In patients with only 20% weight loss after gastric-bypass operations the postprandial PYY and GLP-1 responses are attenuated compared with patients with 40% post-operative weight loss. Moreover, inhibition of the satiety gastrointestinal hormone response with octreotide after gastric bypass increases appetite and food intake. The proposed mechanism behind these findings is that bariatric surgery gives a secretory stimulus to the distal L-cells, resulting in an increased level of gastrointestinal hormones such as PYY and the enteroglucagon family of peptides. As a result, patients have long-term decreased appetite after gastric bypass. The combined effect of exogenous elevation of PYY and GLP-1 reduces food intake more than predicted by individual hormone infusions alone. This combination of gastrointestinal hormone responses might, therefore, contribute to the successful weight loss and its maintenance after bariatric surgery.

On the other hand, changes in ghrelin levels after bariatric surgery are controversial. Ghrelin levels have been reported to be markedly suppressed after gastric bypass, while diet-induced weight loss is associated with increased levels of plasma ghrelin. It was suggested that reduced ghrelin contributes to the weight loss after gastric bypass. Other authors have published conflicting results. Thus, the role of ghrelin after gastric bypass remains unclear. Ghrelin secretion might in fact be modified by other gastrointestinal hormones, the levels of which 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.

Long-term follow-up data on the changes in gastrointestinal hormones after bariatric surgery are still awaited. Surgery modulates a number of the 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

Gastrointestinal hormones have attracted a remarkable amount of research interest in recent years because of their physiological effects on energy balance and appetite effects. Gastric bypass surgery is associated with elevated satiety and satiety-inducing gut hormones. Blocking these hormones reverses the satiety effects. Although surgery has been shown to be beneficial for the time being, it carries a risk for complications for patients. Bariatric surgery may thus be used as a model to understand physiological weight loss. This knowledge may help to guide future surgical and non-surgical weight-loss treatments.

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