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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

Obesity is a major health problem that is associated with increased morbidity and mortality[1]. Its personal, social and economic consequences can be devastating[1–3]. Substantial research efforts are being directed towards the development of successful weight-loss therapies. Consequently, the understanding of neuroendocrine regulation of food intake and weight gain, especially in relation to the role of gut hormones, has substantially increased over recent years, but new therapies are still awaited[4–6]. Current anti-obesity drugs are moderately effective at achieving weight loss, but considerable adverse effects can occur. Presently, the only effective treatment with a proven mortality benefit is bariatric surgery[7,8]. The mechanisms underlying the effectiveness of these surgical techniques are not completely understood but alterations in circulating gut hormone levels have been shown to be an important factor[9–11]. The gut–brain axis refers in part to gut hormones communicating information from the gastrointestinal tract to the appetite centres within the central nervous system. Changes in these hormones following bariatric surgery may partly explain the mechanism by which surgery reduces appetite and sustains weight loss.

Bariatric surgery

Bariatric surgery, also known as weight-loss surgery, refers to the various surgical procedures performed to treat obesity by modification of 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/m^2 with an obesity-related comorbidity or patients with a BMI ≥ 40 kg/m^2 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

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

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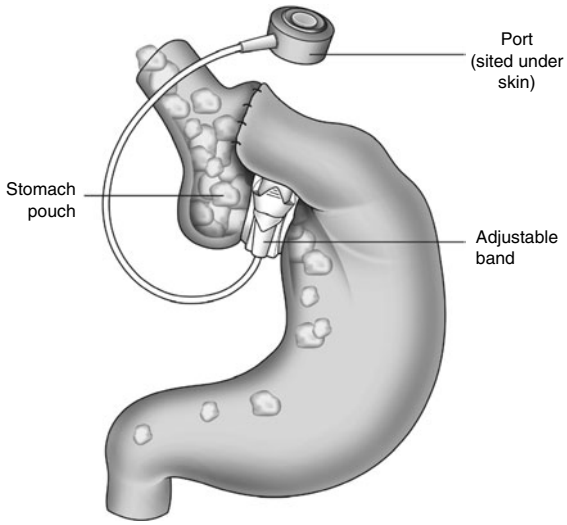

Fig. 1. Gastric banding, a restrictive procedure performed to treat obesity.

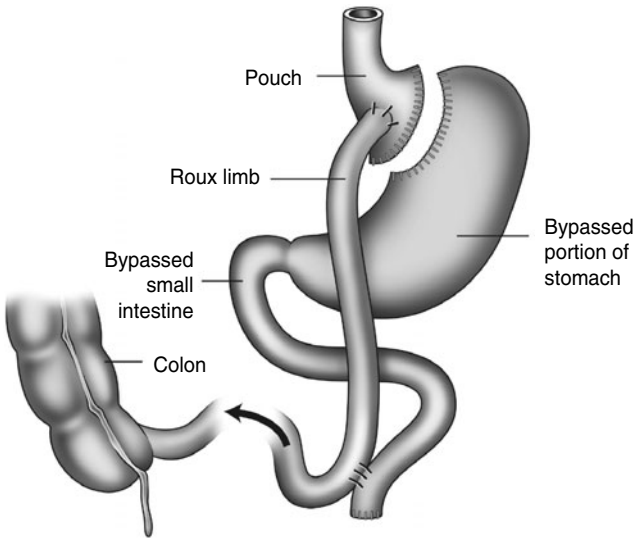

Fig. 2. Roux-en-Y gastric bypass, a bypass procedure performed to treat obesity.

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

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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

Glucagon-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[50–52]. 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[49]. 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[64,65]. 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[65].

Peptide YY

As a thirty-six-amino acid peptide PYY is a member of the pancreatic polypeptide family[66]. 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 co-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–brainstem–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[84]. 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 gallbladder 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

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K-cells in the duodenum and proximal jejunum within minutes after food ingestion[87]. The main stimulus for GIP secretion is the presence of glucose and fat[88]. GIP promotes energy storage by direct actions on adipose tissue. The peptides exert several anabolic adipocyte actions[88,89] as well as lipolytic effects. GIP-receptor-knock-out mice have lower adipocyte mass and display a resistance to diet-induced obesity[90]. GIP on its own has no acute impact on food intake[87], 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[91]. GIP levels have been found to be elevated in obese individuals[87].

Gut hormones and appetite after bariatric surgery

Changes in appetite are evident within days of bariatric surgery[10]. Postprandial levels of gastrointestinal hormones that induce satiety, such as GLP-1 and PYY, are elevated after gastric bypass surgery[92], but not after gastric banding[93]. It has been shown that hunger is reduced and satiety is elevated if gastric bands are optimally inflated[13]. These changes in appetite appear independent of any gut hormone alterations[93]. Administration of octreotide, which would inhibit gut hormone responses, does not affect food intake after gastric banding[93]. Thus, non-hormonal mechanisms have been suggested[93]. In contrast, studies have demonstrated that postprandial PYY and GLP-1 levels start rising as early as 2 d after gastric bypass and can remain elevated for many months after surgery[10,11]. 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[10]. Moreover, inhibition of the satiety gastrointestinal hormone response with octreotide after gastric bypass increases appetite and food intake[10]. 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[93]. 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[94]. 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[43]. It was suggested that reduced ghrelin contributes to the weight loss after gastric bypass[43]. Other authors have published conflicting results[95–99]. 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[100].

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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References

1. Visscher TL & Seidell JC (2001) The public health impact of obesity. *Annu Rev Public Health* **22**, 355–375.
2. Allison DB & Saunders SE (2000) Obesity in North America. An overview. *Med Clin North Am* **84**, 305–332.
3. Hedley AA, Ogden CL, Johnson CL *et al.* (2004) Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA* **291**, 2847–2850.
4. Kaplan LM (2005) Pharmacological therapies for obesity. *Gastroenterol Clin North Am* **34**, 91–104.
5. Thearle M & Aronne LJ (2003) Obesity and pharmacologic therapy. *Endocrinol Metab Clin North Am* **32**, 1005–1024.
6. Yanovski SZ & Yanovski JA (2002) Obesity. *N Engl J Med* **346**, 591–602.
7. Adams TD, Gress RE, Smith SC *et al.* (2007) Long-term mortality after gastric bypass surgery. *N Engl J Med* **357**, 753–761.
8. Sjostrom L, Narbro K, Sjostrom CD *et al.* (2007) Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* **357**, 741–752.
9. Borg CM, le Roux CW, Ghatei MA *et al.* (2006) Progressive rise in gut hormone levels after Roux-en-Y gastric bypass suggests gut adaptation and explains altered satiety. *Br J Surg* **93**, 210–215.
10. le Roux CW, Welbourn R, Werling M *et al.* (2007) Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. *Ann Surg* **246**, 780–785.
11. Naslund E, Gryback P, Hellstrom PM *et al.* (1997) Gastrointestinal hormones and gastric emptying 20 years after

https://doi.org/10.1017/S0029665109001256 Published online by Cambridge University Press

jejunoileal bypass for massive obesity. *Int J Obes Relat Metab Disord* **21**, 387–392.
12. National Institute for Health and Clinical Excellence (2006) *Obesity Guidance on the Prevention, Identification, Assessment and Management of Overweight and Obesity in Adults and Children. NICE Clinical Guideline* 43. London: NICE.
13. Dixon AF, Dixon JB & O'Brien PE (2005) Laparoscopic adjustable gastric banding induces prolonged satiety: a randomized blind crossover study. *J Clin Endocrinol Metab* **90**, 813–819.
14. Buchwald H, Husemann B, Leutenegger AF *et al.* (1986) Morbid obesity – surgical treatment – when and how? *Langenbecks Arch Chir* **368**, 73–79.
15. Buchwald H (2005) Bariatric surgery for morbid obesity: health implications for patients, health professionals, and third-party payers. *J Am Coll Surg* **200**, 593–604.
16. Maggard MA, Shugarman LR, Suttorp M *et al.* (2005) Meta-analysis: surgical treatment of obesity. *Ann Intern Med* **142**, 547–559.
17. Pilkington TR, Gazet JC, Ang L *et al.* (1976) Explanations for weight loss after ileojejunal bypass in gross obesity. *Br Med J* **1**, 1504–1505.
18. Adams TD, Gress RE, Smith SC *et al.* (2007) Long-term mortality after gastric bypass surgery. *N Engl J Med* **357**, 753–761.
19. Sjostrom L, Lindroos AK, Peltonen M *et al.* (2004) Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* **351**, 2683–2693.
20. Ojo P, Asiyanbola B, Valin E *et al.* (2008) Post discharge prophylactic anticoagulation in gastric bypass patient – how safe? *Obes Surg* **18**, 791–796.
21. Westling A, Bergqvist D, Bostrom A *et al.* (2002) Incidence of deep venous thrombosis in patients undergoing obesity surgery. *World J Surg* **26**, 470–473.
22. Encinosa WE, Bernard DM, Chen CC *et al.* (2006) Healthcare utilization and outcomes after bariatric surgery. *Med Care* **44**, 706–712.
23. Flum DR, Salem L, Elrod JA *et al.* (2005) Early mortality among Medicare beneficiaries undergoing bariatric surgical procedures. *JAMA* **294**, 1903–1908.
24. Wren AM, Seal LJ, Cohen MA *et al.* (2001) Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab* **86**, 5992.
25. Cone RD, Cowley MA, Butler AA *et al.* (2001) The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. *Int J Obes Relat Metab Disord* **25**, Suppl. 5, S63–S67.
26. Schwartz MW, Woods SC, Porte D Jr *et al.* (2000) Central nervous system control of food intake. *Nature* **404**, 661–671.
27. Balasubramaniam A, Mullins DE, Lin S *et al.* (2006) Neuropeptide Y (NPY) Y4 receptor selective agonists based on NPY(32–36): development of an anorectic Y4 receptor selective agonist with picomolar affinity. *J Med Chem* **49**, 2661–2665.
28. Larsen PJ & Kristensen P (1997) The neuropeptide Y (Y4) receptor is highly expressed in neurones of the rat dorsal vagal complex. *Brain Res Mol Brain Res* **48**, 1–6.
29. Flier JS (2004) Obesity wars: molecular progress confronts an expanding epidemic. *Cell* **116**, 337–350.
30. Grill HJ & Smith GP (1988) Cholecystokinin decreases sucrose intake in chronic decerebrate rats. *Am J Physiol* **254**, R853–R856.
31. Ellacott KL, Halatchev IG & Cone RD (2006) Interactions between gut peptides and the central melanocortin system in the regulation of energy homeostasis. *Peptides* **27**, 340–349.
32. Schwartz MW, Woods SC, Seeley RJ *et al.* (2003) Is the energy homeostasis system inherently biased toward weight gain? *Diabetes* **52**, 232–238.
33. Leibel RL, Rosenbaum M & Hirsch J (1995) Changes in energy expenditure resulting from altered body weight. *N Engl J Med* **332**, 621–628.
34. Brady LS, Smith MA, Gold PW *et al.* (1990) Altered expression of hypothalamic neuropeptide mRNAs in food-restricted and food-deprived rats. *Neuroendocrinology* **52**, 441–447.
35. Murakami N, Hayashida T, Kuroiwa T *et al.* (2002) Role for central ghrelin in food intake and secretion profile of stomach ghrelin in rats. *J Endocrinol* **174**, 283–288.
36. Wren AM, Small CJ, Abbott CR *et al.* (2001) Ghrelin causes hyperphagia and obesity in rats. *Diabetes* **50**, 2540–2547.
37. Nagaya N, Moriya J, Yasumura Y *et al.* (2004) Effects of ghrelin administration on left ventricular function, exercise capacity, and muscle wasting in patients with chronic heart failure. *Circulation* **110**, 3674–3679.
38. Nagaya N, Itoh T, Murakami S *et al.* (2005) Treatment of cachexia with ghrelin in patients with COPD. *Chest* **128**, 1187–1193.
39. Neary NM, Small CJ, Wren AM *et al.* (2004) Ghrelin increases energy intake in cancer patients with impaired appetite: acute, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* **89**, 2832–2836.
40. Cummings DE, Purnell JQ, Frayo RS *et al.* (2001) A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes* **50**, 1714–1719.
41. le Roux CW, Neary NM, Halsey TJ *et al.* (2005) Ghrelin does not stimulate food intake in patients with surgical procedures involving vagotomy. *J Clin Endocrinol Metab* **90**, 4521–4524.
42. Druce MR, Wren AM, Park AJ *et al.* (2005) Ghrelin increases food intake in obese as well as lean subjects. *Int J Obes (Lond)* **29**, 1130–1136.
43. Cummings DE, Weigle DS, Frayo RS *et al.* (2002) Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* **346**, 1623–1630.
44. English PJ, Ghatei MA, Malik IA *et al.* (2002) Food fails to suppress ghrelin levels in obese humans. *J Clin Endocrinol Metab* **87**, 2984.
45. le Roux CW, Patterson M, Vincent RP *et al.* (2005) Postprandial plasma ghrelin is suppressed proportional to meal calorie content in normal-weight but not obese subjects. *J Clin Endocrinol Metab* **90**, 1068–1071.
46. Holst JJ (2004) On the physiology of GIP and GLP-1. *Horm Metab Res* **36**, 747–754.
47. Larsen PJ, Tang-Christensen M & Jessop DS (1997) Central administration of glucagon-like peptide-1 activates hypothalamic neuroendocrine neurons in the rat. *Endocrinology* **138**, 4445–4455.
48. Crawley JN & Beinfeld MC (1983) Rapid development of tolerance to the behavioural actions of cholecystokinin. *Nature* **302**, 703–706.
49. Abbott CR, Monteiro M, Small CJ *et al.* (2005) The inhibitory effects of peripheral administration of peptide YY(3–36) and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway. *Brain Res* **1044**, 127–131.
50. Feinle C, Chapman IM, Wishart J *et al.* (2002) Plasma glucagon-like peptide-1 (GLP-1) responses to duodenal fat and glucose infusions in lean and obese men. *Peptides* **23**, 1491–1495.
51. Fukase N, Igarashi M, Takahashi H *et al.* (1993) Hypersecretion of truncated glucagon-like peptide-1 and gastric

https://doi.org/10.1017/S0029665109001256 Published online by Cambridge University Press

inhibitory polypeptide in obese patients. *Diabet Med* **10**, 44–49.
52. Verdich C, Toubro S, Buemann B *et al.* (2001) The role of postprandial releases of insulin and incretin hormones in meal-induced satiety – effect of obesity and weight reduction. *Int J Obes Relat Metab Disord* **25**, 1206–1214.
53. Edwards CM, Todd JF, Mahmoudi M *et al.* (1999) Glucagon-like peptide 1 has a physiological role in the control of postprandial glucose in humans: studies with the antagonist exendin 9–39. *Diabetes* **48**, 86–93.
54. Kreymann B, Williams G, Ghatei MA *et al.* (1987) Glucagon-like peptide-1 7–36: a physiological incretin in man. *Lancet* **ii**, 1300–1304.
55. Edwards CM, Stanley SA, Davis R *et al.* (2001) Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am J Physiol Endocrinol Metab* **281**, E155–E161.
56. Gutzwiller JP, Goke B, Drewe J *et al.* (1999) Glucagon-like peptide-1: a potent regulator of food intake in humans. *Gut* **44**, 81–86.
57. O'Shea D, Gunn I, Chen X *et al.* (1996) A role for central glucagon-like peptide-1 in temperature regulation. *Neuroreport* **7**, 830–832.
58. Turton MD, O'Shea D, Gunn I *et al.* (1996) A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* **379**, 69–72.
59. Ruiz-Grande C, Alarcon C, Merida E *et al.* (1992) Lipolytic action of glucagon-like peptides in isolated rat adipocytes. *Peptides* **13**, 13–16.
60. Villanueva-Penacarrillo ML, Marquez L, Gonzalez N *et al.* (2001) Effect of GLP-1 on lipid metabolism in human adipocytes. *Horm Metab Res* **33**, 73–77.
61. Todd JF, Edwards CM, Ghatei MA *et al.* (1998) Subcutaneous glucagon-like peptide-1 improves postprandial glycaemic control over a 3-week period in patients with early type 2 diabetes. *Clin Sci (Lond)* **95**, 325–329.
62. Guerci B & Martin CS (2008) Exenatide: its position in the treatment of type 2 diabetes. *Ann Endocrinol (Paris)* **69**, 201–209.
63. Soltani N, Kumar M, Glinka Y *et al.* (2007) In vivo expression of GLP-1/IgG-Fc fusion protein enhances beta-cell mass and protects against streptozotocin-induced diabetes. *Gene Ther* **14**, 981–988.
64. DeFronzo RA, Ratner RE, Han J *et al.* (2005) Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* **28**, 1092–1100.
65. Kendall DM, Riddle MC, Rosenstock J *et al.* (2005) Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* **28**, 1083–1091.
66. Tatemoto K & Mutt V (1980) Isolation of two novel candidate hormones using a chemical method for finding naturally occurring polypeptides. *Nature* **285**, 417–418.
67. Adrian TE, Ferri GL, Bacarese-Hamilton AJ *et al.* (1985) Human distribution and release of a putative new gut hormone, peptide YY. *Gastroenterology* **89**, 1070–1077.
68. Ali-Rachedi A, Varndell IM, Adrian TE *et al.* (1984) Peptide YY (PYY) immunoreactivity is co-stored with glucagon-related immunoreactants in endocrine cells of the gut and pancreas. *Histochemistry* **80**, 487–491.
69. Adrian TE, Savage AP, Sagor GR *et al.* (1985) Effect of peptide YY on gastric, pancreatic, and biliary function in humans. *Gastroenterology* **89**, 494–499.
70. Allen JM, Fitzpatrick ML, Yeats JC *et al.* (1984) Effects of peptide YY and neuropeptide Y on gastric emptying in man. *Digestion* **30**, 255–262.
71. le Roux CW, Batterham RL, Aylwin SJ *et al.* (2006) Attenuated peptide YY release in obese subjects is associated with reduced satiety. *Endocrinology* **147**, 3–8.
72. Chelikani PK, Haver AC & Reidelberger RD (2005) Intravenous infusion of peptide YY(3–36) potently inhibits food intake in rats. *Endocrinology* **146**, 879–888.
73. Degen L, Oesch S, Casanova M *et al.* (2005) Effect of peptide YY3–36 on food intake in humans. *Gastroenterology* **129**, 1430–1436.
74. Koegler FH, Enriori PJ, Billes SK *et al.* (2005) Peptide YY(3–36) inhibits morning, but not evening, food intake and decreases body weight in rhesus macaques. *Diabetes* **54**, 3198–3204.
75. Tschop M, Castaneda TR, Joost HG *et al.* (2004) Physiology: does gut hormone PYY3–36 decrease food intake in rodents? *Nature* **430**, 1.
76. Boey D, Lin S, Karl T *et al.* (2006) Peptide YY ablation in mice leads to the development of hyperinsulinaemia and obesity. *Diabetologia* **49**, 1360–1370.
77. Batterham RL, Cowley MA, Small CJ *et al.* (2002) Gut hormone PYY(3–36) physiologically inhibits food intake. *Nature* **418**, 650–654.
78. Acuna-Goycolea C & van den Pol AN (2005) Peptide YY(3–36) inhibits both anorexigenic proopiomelanocortin and orexigenic neuropeptide Y neurons: implications for hypothalamic regulation of energy homeostasis. *J Neurosci* **25**, 10510–10519.
79. Abbott CR, Small CJ, Kennedy AR *et al.* (2005) Blockade of the neuropeptide Y Y2 receptor with the specific antagonist BIIE0246 attenuates the effect of endogenous and exogenous peptide YY(3–36) on food intake. *Brain Res* **1043**, 139–144.
80. Batterham RL, Cohen MA, Ellis SM *et al.* (2003) Inhibition of food intake in obese subjects by peptide YY3–36. *N Engl J Med* **349**, 941–948.
81. White NE, Dhillo WS, Liu YL *et al.* (2008) Co-administration of SR141716 with peptide YY3–36 or oxyntomodulin has additive effects on food intake in mice. *Diabetes Obes Metab* **10**, 167–170.
82. Batterham RL, Heffron H, Kapoor S *et al.* (2006) Critical role for peptide YY in protein-mediated satiation and body-weight regulation. *Cell Metab* **4**, 223–233.
83. Greenough A, Cole G, Lewis J *et al.* (1998) Untangling the effects of hunger, anxiety, and nausea on energy intake during intravenous cholecystokinin octapeptide (CCK-8) infusion. *Physiol Behav* **65**, 303–310.
84. Naslund E, King N, Mansten S *et al.* (2004) Prandial subcutaneous injections of glucagon-like peptide-1 cause weight loss in obese human subjects. *Br J Nutr* **91**, 439–446.
85. Adrian TE, Savage AP, Bacarese-Hamilton AJ *et al.* (1986) Peptide YY abnormalities in gastrointestinal diseases. *Gastroenterology* **90**, 379–384.
86. Di Francesco V, Zamboni M, Dioli A *et al.* (2005) Delayed postprandial gastric emptying and impaired gallbladder contraction together with elevated cholecystokinin and peptide YY serum levels sustain satiety and inhibit hunger in healthy elderly persons. *J Gerontol A Biol Sci Med Sci* **60**, 1581–1585.
87. Baggio LL & Drucker DJ (2007) Biology of incretins: GLP-1 and GIP. *Gastroenterology* **132**, 2131–2157.
88. Creutzfeldt W, Ebert R, Willms B *et al.* (1978) Gastric inhibitory polypeptide (GIP) and insulin in obesity: increased response to stimulation and defective feedback control of serum levels. *Diabetologia* **14**, 15–24.
89. Salera M, Giacomoni P, Pironi L *et al.* (1982) Gastric inhibitory polypeptide release after oral glucose: relationship to glucose intolerance, diabetes mellitus, and obesity. *J Clin Endocrinol Metab* **55**, 329–336.

https://doi.org/10.1017/S0029665109001256 Published online by Cambridge University Press

90. Miyawaki K, Yamada Y, Ban N *et al.* (2002) Inhibition of gastric inhibitory polypeptide signaling prevents obesity. *Nat Med* **8**, 738–742.
91. Ding WG & Gromada J (1997) Protein kinase A-dependent stimulation of exocytosis in mouse pancreatic beta-cells by glucose-dependent insulinotropic polypeptide. *Diabetes* **46**, 615–621.
92. Borg CM, le Roux CW, Ghatei MA *et al.* (2006) Progressive rise in gut hormone levels after Roux-en-Y gastric bypass suggests gut adaptation and explains altered satiety. *Br J Surg* **93**, 210–215.
93. le Roux CW, Aylwin SJ, Batterham RL *et al.* (2006) Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. *Ann Surg* **243**, 108–114.
94. Neary NM, Small CJ, Druce MR *et al.* (2005) Peptide YY3–36 and glucagon-like peptide-17–36 inhibit food intake additively. *Endocrinology* **146**, 5120–5127.
95. Couce ME, Cottam D, Esplen J *et al.* (2006) Is ghrelin the culprit for weight loss after gastric bypass surgery? A negative answer. *Obes Surg* **16**, 870–878.
96. Holdstock C, Engstrom BE, Ohrvall M *et al.* (2003) Ghrelin and adipose tissue regulatory peptides: effect of gastric bypass surgery in obese humans. *J Clin Endocrinol Metab* **88**, 3177–3183.
97. Lee H, Te C, Koshy S *et al.* (2006) Does ghrelin really matter after bariatric surgery? *Surg Obes Relat Dis* **2**, 538–548.
98. Mancini MC, Costa AP, de Melo ME *et al.* (2006) Effect of gastric bypass on spontaneous growth hormone and ghrelin release profiles. *Obesity (Silver Spring)* **14**, 383–387.
99. Stenstrom B, Zhao CM, Tommeras K *et al.* (2006) Is gastrin partially responsible for body weight reduction after gastric bypass? *Eur Surg Res* **38**, 94–101.
100. Rubino F & Gagner M (2002) Weight loss and plasma ghrelin levels. *N Engl J Med* **347**, 1379–1381.

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