

BAYLISS–STARLING PRIZE LECTURE

Can Bayliss and Starling gut hormones cure a worldwide pandemic?

R. V. Scott, T. M. Tan and S. R. Bloom

Division of Diabetes, Endocrinology and Metabolism, Imperial College London, Hammersmith Hospital, Du Cane Road, London, W12 0NN, UK

Abstract Bayliss and Starling first coined the term ‘hormone’ with reference to secretin, a substance they found that was produced by the gut, but released into the blood stream to act at a distance. The intestine is now known as the largest endocrine organ in the body, and it produces numerous hormones with a wide range of functions. These include controlling appetite and energy homeostasis. Obesity is one of the greatest health threats facing the world today. At present, the only successful treatment is surgery. Bariatric procedures such as the Roux-en-Y bypass work by elevating gut hormones that induce satiety. Significant research has gone into producing versions of these hormones that can be delivered therapeutically to treat obesity. This review looks at the role of gut hormones in obesity, and the development of gut hormone-derived obesity treatments.

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Corresponding author R. V. Scott: Department of Metabolic Medicine, Imperial College London, Hammersmith Hospital, London W12 0NN, UK. Email: r.scott@imperial.ac.uk

Abbreviations CCK, cholecystokinin; DPP-4, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide-1; GOAT, ghrelin-O-transferase; I.C.V., intracerebroventricular; PP, pancreatic polypeptide; PP-fold, pancreatic polypeptide fold family; PYY, peptide tyrosine tyrosine.

Introduction

Obesity is a problem of balance: too many calories being consumed, insufficient energy being expended. It is physiological, i.e. if you didn’t put on weight in the summer, you might die in the winter. The bad news is that it is now ‘summer’ all the time. The statistics for the current chronic energy imbalance are staggering. The 2013 NHS report on obesity (The Health and Social Care Information Centre, 2013) highlights the continuing expansion of the

nation’s waistline, with 65% of men and 58% of women being overweight or obese in 2011. The number of hospital admissions where obesity is the primary diagnosis has increased 11-fold over a decade (The Health and Social Care Information Centre, 2013). This trend is not limited to the United Kingdom: World Health Organisation studies show this is a global phenomenon (Global Health Observatory, 2008). Obesity has consequences for physical health, being associated with a rise in cases of diabetes, strokes and heart attacks, but also has a financial impact,

Professor Sir Steven Bloom is the Head of Division for Diabetes, Endocrinology and Metabolism, Chair of the academic Section of Endocrinology and Investigative Medicine at Imperial College London, and Lead Clinician for Clinical Chemistry at Imperial College Healthcare NHS Trust. He leads a team of more than forty researchers, investigating the physiology of hormones and peptides within the central nervous system, and in the periphery. **Dr Tricia Tan** is a Consultant in Metabolic Medicine and Endocrinology at Imperial College Healthcare NHS Trust. She qualified in 1996 from Manchester University and trained in Endocrinology and Diabetes Mellitus in London. She has over a decade of experience in experimental research in the physiology of gut hormones, and spearheads the Division of Investigative Medicine’s current Phase I trials of analogues of Pancreatic Polypeptide, peptide YY, GLP-1 and glucagon as treatments for Diabetes and Obesity. **Dr Rebecca Scott** is a Specialist Registrar in Diabetes and Endocrinology. She has recently started a PhD at Imperial College London, investigating the role of gut hormones and energy expenditure.



through increased use of health services, and reduction in employment levels. It is estimated that the Actual Total Costs of Obesity in the UK by 2050 will be £45.5 billion per year (McPherson *et al.* 2007). The obese also usually don't want to be overweight, and being so can make them feel miserable.

Current treatments for obesity

Diet, exercise and life-style modifications remain the first line treatments for obesity. A large meta-analysis has shown exercise advice alone has, at 6 or 12 months, no significant impact on body weight. While dieting can cause a 5% weight loss at 6 months, this drops to 3% at 48 months (Franz *et al.* 2007). Combined, diet and exercise has been reported to cause 8.5% weight loss at 6 months, though this is limited to 4% by 48 months (Franz *et al.* 2007).

The surgical treatment of obesity is well-established and highly effective, with weight loss of up to 18% at 20 years after the initial procedure (Picot *et al.* 2009; Sjöström, 2013). Consequently a number of clinical bodies recommend bariatric surgery as the first line treatment for certain cases of obesity (NICE, 2006; Pories *et al.* 2010; Cummings & Cohen, 2014). But bariatric surgery is not without risk: the mortality rate is between 0.1 and 1.5% (Buchwald *et al.* 2007). Furthermore the cost of bariatric surgery, and the limited number of surgeons performing it, prevents it being a panacea for the obesity epidemic at least in the UK.

Pharmacological treatment of obesity within Europe is limited to orlistat. This is a pancreatic lipase inhibitor that prevents fat absorption within the gut. However, its effectiveness is poor, with the average weight loss being less than 3%, and its use is often accompanied by debilitating and socially undesirable gastrointestinal side-effects (Rucker *et al.* 2007). Other treatments, such as sibutramine and rimonabant, have been withdrawn due to psychiatric and cardiovascular effects (Christensen *et al.* 2007; James *et al.* 2010), and new treatments, notably Qsymia and Belviq, though much feted on their release, have proven unpopular, due to potentially serious side-effects, with both regulatory bodies and physicians in the USA, where they have been granted a licence. This combination of the inefficacy and concerns over side-effects, has caused a fall in the number of prescriptions dispensed for the treatment of obesity in recent years (The Health and Social Care Information Centre, 2013). It is in view of this paucity of viable options that gut hormones may offer a solution.

Control of appetite

The control of appetite requires the interaction of a number of different organs and physiological processes

(Fig. 1). Acutely, food consumption is regulated by activation of gut mechanoreceptors, changes in nutrient concentration within the plasma, and alteration in gut hormone levels. Longer term adiposity signals, such as leptin, also regulate food consumption (Flynn *et al.* 1998; Farooqi *et al.* 2007). In addition to these homeostatic mechanisms, a number of cultural and hedonistic associations with feeding affect food intake. Neuronal circuits that control feeding comprise not only traditional regulatory structures within the brain, such as the hypothalamus and the brainstem, but also the reward pathways of the cortico-limbic system within the brain (Berthoud, 2012). Gut hormones can influence all of these aspects of food intake.

Overview of gut hormones that affect energy homeostasis

The first indication that gut hormones might regulate appetite was demonstrated in 1937 by N. F. MacLagan. He was trying to understand the control of appetite and injected enterogastrone, a crude preparation of ground-up intestine, into rabbits. He found that for an hour after injection, enterogastrone reduced food intake by almost 30% in the animals (MacLagan, 1937).

Thirty years later, Gerard Smith and colleagues started the first systematic investigation in this area. They undertook an elegant programme of experiments to look at the effect of cholecystikinin (CCK) on food intake. They showed that an intraperitoneal injection of CCK into fasted rats inhibited food intake by 50% over the first 30 min (Gibbs *et al.* 1973a). This anorectic effect has since been replicated in subjects as diverse as sheep and obese men. Smith's group then investigated the mechanism by which CCK stopped eating. The normal behavioural sequence of rats who feed to satiety is characterised by a rapid bout of feeding, followed by a period of grooming and sleeping (Gibbs *et al.* 1973b). Sham-fed rats, who have open gastric fistulas, feed continuously, without showing the behavioural pattern of satiety. Shutting the fistulas terminates feeding, and elicits the pattern of satiety behaviour; a single injection of CCK causes the same pattern of behaviour (Gibbs *et al.* 1973b). CCK does not affect the motor aspects of eating (Gibbs *et al.* 1997), nor cause any aversion to food, in either rats or man (Kissileff *et al.* 1981; Pi-Sunyer *et al.* 1982; Gibbs *et al.* 1997). Together, these results confirm CCK as a physiological satiety signal. However, other studies question CCK's utility as an obesity therapy. Continuous administration of CCK for 7–14 days using subcutaneous pumps in rats failed to reduce food intake or body weight compared to saline controls (Crawley & Beinfeld, 1983). Moreover, within 4 h of CCK exposure, these rats were resistant to an acute CCK challenge, at a dose of 5 $\mu\text{g kg}^{-1}$ that in naive

Table 1. Summary of gut hormones involved in energy homeostasis

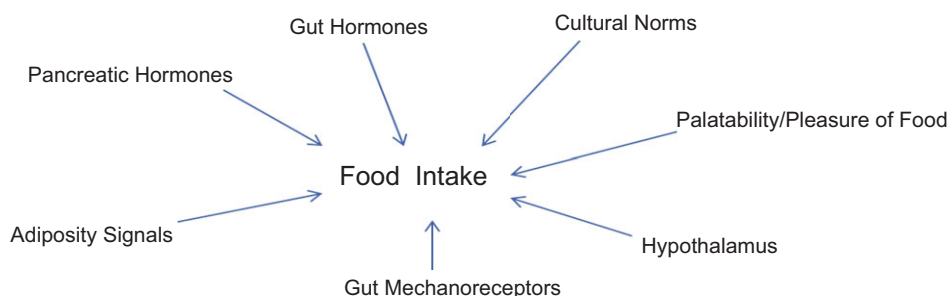
Hormone	Peptide family	Produced by	Activated by	Receptors
Cholecystokinin (CCK)	—	L cells in the intestine	—	CCK1r and CCK2r
Glucagon-like peptide-1 (GLP-1)	Preproglucagon derivative	L cells in the intestine	—	GLP-1r
Glucagon (GCG)	Preproglucagon derivative	α cells of the pancreas	—	GCGr
Oxyntomodulin	Preproglucagon derivative	—	—	GCGr and GLP-1r
Peptide tyrosinetyrosine (PYY)	PP-fold	L cells in the intestine	DPP-4	Y1, Y2 and Y5 (Y2 specifically when activated)
Pancreatic polypeptide (PP)	PP-fold	PP cells of the pancreas	—	Y4
Amylin (IAPP)	—	β cells of the pancreas	—	AMY1a, AMY2a and AMY3a
Ghrelin	—	X/A-like cells in the stomach	GOAT	GHSr

rats elicited satiety (Crawley & Beinfeld, 1983). This rapid development of tolerance to the satiety effects of CCK limits its therapeutic potential. It has also been shown to cause both acute pancreatitis and pancreatic cancer.

Since then, a number of other hormones have been found to signal satiety to the brain. At the same time that Smith and others were investigating CCK, work by Joel Habener at Massachusetts General Hospital, and Graeme Bell and colleagues at Lilly Research Labs in Indianapolis, led to the discovery of glucagon-like peptide-1 (GLP-1). This is released from the L cells of the small intestine, produced from the preproglucagon gene. Its role as an incretin was established early on (Schmidt *et al.* 1985), but the discovery of GLP-1 receptors within the brain suggested the possibility of functions beyond that of an incretin. GLP-1 administered intracerebroventricularly (i.c.v.) in rats reduced food intake in a dose-dependent manner (Turton *et al.* 1996) (Fig. 2). GLP-1 elicits the typical satiety pattern of behaviour (Turton *et al.* 1996). Jens Holst's group administered GLP-1 via a

subcutaneous infusion to both lean and obese human subjects, and demonstrated an increase in the sensation of satiety, a reduction in the sensation of hunger, and a reduction in caloric intake at a subsequent meal (Flint *et al.* 1998; Näslund *et al.* 1999). A meta-analysis by Verdich *et al.* confirmed that GLP-1 reduces food intake in a dose-dependent manner in lean and overweight subjects (Verdich *et al.* 2001). Importantly, GLP-1 retains its anorectic effects during chronic exposure. GLP-1 administered at $4.8 \text{ pmol kg}^{-1} \text{ min}$ for 6 weeks using subcutaneous insulin pumps caused an average loss of 2 kg, or 2% body weight (Zander *et al.* 2002).

Like GLP-1, oxyntomodulin is a product of the preproglucagon gene, released from the L cells of the intestine. It consists of a glucagon molecule with a C-terminal peptide extension (Bataille *et al.* 1981b), and can activate both the glucagon and GLP-1 receptor, albeit more weakly than either cognate ligand (Baldisserra *et al.* 1988; Gros *et al.* 1993). In line with its activity at the GLP-1 receptor, oxyntomodulin acutely reduces feeding when

**Figure 1. Diagram of structures involved in control of food intake**

administered both i.c.v. and peripherally in rats. Its anorectic effects may be mediated by central structures, as 3 nmol kg⁻¹ of peptide significantly reduced food intake when administered i.c.v. compared to 30 nmol kg⁻¹ when administered peripherally (Dakin *et al.* 2001, 2004). Oxyntomodulin also reduces food intake in man: subjects taught to administer 400 nmol of oxyntomodulin subcutaneously prior to each meal lost an average of 2.4% body weight over 4 weeks, and demonstrated a reduction in caloric intake at a test meal following an injection of oxyntomodulin (Wynne *et al.* 2005). In addition to reducing food intake, oxyntomodulin increases energy expenditure. A pair feeding study was undertaken using three groups of rats: oxyntomodulin administered i.c.v., an *ad libitum*-fed saline control group, and a group administered saline i.c.v., but pair-fed to the oxyntomodulin group (Dakin *et al.* 2002). Over 7 days, both the experimental and pair-fed groups ate identically, but much less than the control group; however, the experimental group lost significantly more weight than the pair-fed animals. This finding has been supported in human studies, where those subjects who self-administered oxyntomodulin increased their activity-related energy expenditure by almost 30% over 4 weeks (Wynne *et al.* 2006). The exact mechanism by which oxyntomodulin increases energy expenditure has still to be elucidated; a recent study by Lockie *et al.* showed an increase in brown adipose tissue activation and thermogenesis following acute i.c.v. administration of oxyntomodulin in mice, which might mediate some weight loss effects (Lockie *et al.* 2012). The relative contributions of the glucagon and GLP-1 receptors to the effects of oxyntomodulin on food intake and energy expenditure effects are not firmly established (Baggio *et al.* 2004; Pocai *et al.* 2009; Kosinski *et al.* 2012; Lockie *et al.* 2012). Nevertheless, the dual action of

oxyntomodulin makes it an attractive target for obesity therapies.

A third hormone produced by the L cells is peptide tyrosine tyrosine (PYY). This is a member of the pancreatic polypeptide (PP) family, a group containing PP, PYY and the neurotransmitter neuropeptide Y (NPY), and defined by a common hair-pin-fold structure. The PP-fold peptides act on the Y receptor superfamily. PYY is released as a 36 residue peptide, PYY(1–36), which can activate the Y1, Y2 and Y5 receptors; however, it is cleaved to PYY(3–36) within the plasma by dipeptidyl peptidase IV (DPP-4); Keire *et al.* 2000; Kanatani *et al.* 2000). Activated PYY levels peak soon after food is ingested, characteristic of a signal of satiety (Adrian *et al.* 1985), and they rise in proportion to the size and caloric content of the meal consumed (Adrian *et al.* 1985). Its role as a satiety signal has been confirmed *in vivo*. Intraperitoneal injections of PYY(3–36) into rats reduced food intake in a dose-dependent fashion (Batterham *et al.* 2002). In humans, a 90 min peripheral infusion of PYY(3–36) at a dose of 0.8 pmol kg⁻¹ min⁻¹ produced PYY levels comparable to those seen after eating; this reduced food intake by 33% over a 24 h period when compared to the saline control group (Batterham *et al.* 2002). Obesity is associated with lower fasting levels of PYY(3–36), and impaired post-prandial secretion of the hormone (Batterham *et al.* 2003); however, obesity does not appear to cause resistance to the action of PYY, as a similar infusion of PYY(3–36) in obese subjects reduced food intake by 16% over 24 h (Batterham *et al.* 2003).

Pancreatic polypeptide is another PP-fold hormone and satiety signal. It is produced predominantly by the pancreas, but also in small quantities by the distal gut (Adrian *et al.* 1976). Intraperitoneal injections of PP reduce food intake by almost 50% over a 4 h period in both lean and obese *ob/ob* mice (Asakawa *et al.* 2006). A randomised, double-blind, cross-over study infusing saline or pancreatic polypeptide at 10 pmol kg⁻¹ min⁻¹ into healthy human volunteers reduced food intake at a subsequent buffet meal by 21%, and 24 h food intake by 25% (Batterham *et al.* b).

Amylin, also known as islet amyloid polypeptide or IAPP, is a further peptide produced by the pancreas. This is co-secreted with insulin from the β cells, and cleaved from an 89 amino-acid prohormone (Sanke *et al.* 1988). In addition to its effects on insulin release and glycaemic control, studies have looked at the effect of amylin on feeding; these have shown it to have the characteristics of a satiety signal. Acutely, amylin reduces food intake in rats over 8 h in a dose-dependent manner (Chance *et al.* 1991, 1993), and chronic subcutaneous infusions in rats reduced body weight in a dose-dependent manner (Arnelo *et al.* 2000). Amylin has a ready propensity to form insoluble amyloid fibrils, which reduces its solubility, and therefore prevents easy administration of the native peptide.

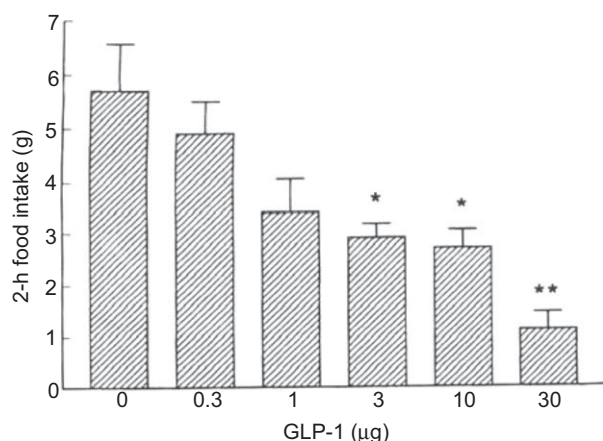


Figure 2. Effect of i.c.v. GLP-1 on food intake

Reproduced from Turton *et al.* (1996) with permission from Macmillan Publishers Ltd.

In contrast to the multitude of hormones mentioned above that suppress appetite, there is only one native hormone that stimulates food intake. Ghrelin is a 28 amino-acid peptide produced by the X/A-like cells of the stomach (Date *et al.* 2000). It is *n*-octanoylated on the third residue (Kojima *et al.* 1999), a reaction catalysed by the enzyme ghrelin-*O*-transferase (GOAT) (Yang *et al.* 2008). Ghrelin binds to the growth hormone secretagogue receptor (GHSr). Ghrelin levels increase during fasting, and fall after eating, suggesting that it acts as a signal to stimulate food intake (Tschöp *et al.* 2000, 2001; Cummings *et al.* 2001); indeed, exogenously administered ghrelin increases food intake in man and rodents (Wren *et al.* 2001a, b). Reducing ghrelin levels, or blocking its effects, may therefore be an alternative strategy to treat obesity.

Bariatric surgery

Bariatric surgery is a highly effective treatment for obesity. Surgical techniques can be loosely divided into two groups: those that are purely restrictive in nature, and those that also contain an element of gastric bypass (Fig. 3). Restrictive techniques, such as gastric banding, work by restricting the quantity of food that can be consumed at any one time. In contrast, bypass surgery alters the normal pathway for food, so digestion occurs further down the gut and, since the density of L cells increases with distance along the small intestine, the release of gut hormones is greater. The most commonly employed bariatric surgery technique contains both restrictive and bypass elements. In a Roux-en-Y gastric bypass, a technique refined from that described by Mason and Ito in 1969, the stomach is divided so that only a small proximal pouch exists, which is then joined to the jejunum. Food therefore bypasses a large portion of the stomach, the duodenum and proximal part of the jejunum. The remaining stomach and duodenum is then itself anastomosed to the jejunum, allowing all intestinal, biliary and pancreatic secretions to enter the lower intestine.

The distinction between the restrictive and bypass surgeries is important: bypass surgery causes greater, sustained weight loss, and can cause rapid improvement in diabetes (Rubino *et al.* 2006; Tice *et al.* 2008; Colquitt *et al.* 2009; Li *et al.* 2014). Though there is an element of malabsorption following gastric bypass, which requires careful monitoring of patients' micronutrient intake, overall malnutrition, as determined by albumin levels, is not the cause of weight loss following surgery (Bradley *et al.* 1977; Odstřil *et al.* 2010; Blume *et al.* 2012). A prospective study by Griffen *et al.* (1977) showed a similar amount of weight loss following a Roux-en-Y bypass to that following the more malabsorptive procedure of jejunoileal bypass (JIB), even though the length of bowel bypassed in the

JIB is fourtimes greater (Griffen *et al.* 1977). Instead, it is thought that the change in secretion of gut hormones, in response to changes in the digestive pathway, leads to the improved weight loss in bypass surgery. Specifically, post-prandial levels of the satiety signals GLP-1, PYY and oxyntomodulin are increased (Korner *et al.* 2009; Beckman *et al.* 2010, LaFerrère *et al.* 2010; Falkén *et al.* 2011; Dirksen *et al.* 2013). The effects of these changes are twofold. The first is an increase in post-prandial satiety, which in combination with gastric pouch size restriction, reduces food intake. The second effect is that the change in hormonal milieu alters food preference. Kenler *et al.* reviewed dietary preferences and caloric intake in patients pre-operatively, and for 2 years following either horizontal gastropasty or Roux-en-Y bypass. The Roux-en-Y group reduced their overall caloric intake by almost 60%, and their intake of sweet food by more than 45% (Kenler *et al.* 1990). Shin *et al.* looked at rodent models of Roux-en-Y bypass and compared food preference as measured by a number of behavioural tests, in surgical, sham-operated, and control rats. They found that the surgery enhanced the rats' liking of low calorie content solutions, and reduced their preference for high fat or sugar food, in a mirroring of the human studies (Shin *et al.* 2011). It is this combination of reduced food intake, and changes in types of food consumed, that leads to the efficacy of gastric bypass surgery at causing sustained weight loss.

Gut hormones as an obesity therapy

The efficacy of gut hormones in *in vivo* and clinical trials, and their role in mediating the weight loss effects of bariatric surgery, makes them attractive targets in obesity therapy. However, there are a number of obstacles to overcome in the production of a viable anti-obesity drug. As discussed, obesity therapies have so far been hamstrung by lack of efficacy and serious side-effects. In developing peptide therapeutics, Maclagan, in 1937, noted two of the major limitations: their 'rather transient' effects, and that they are 'not active by mouth' (Maclagan, 1937). These aspects must be addressed to develop an effective anti-obesity medication.

The half-lives of native gut hormones within the plasma are limited to a few minutes due to degradation by enzymes such as DPP-4 (Schjoldager *et al.* 1988; Lluís *et al.* 1989; Parkes *et al.* 2001). Prolonging the activity of the peptides is therefore essential. The first success in this area came about by chance. John Eng was screening the venom of snakes and lizards when he isolated a family of peptides from the saliva of the gila monster lizard, *Heloderma suspectum* (Eng *et al.* 1992). One of these, exendin-4, has sequence homology with GLP-1, and similar biological effects (Raufman *et al.* 1992). The sequence differences, notably at the N terminal, render it resistant to degradation by

DPP-4. These changes extend its half-life from 5 min to 2 h (Parkes *et al.* 2001; Thum *et al.* 2002). A synthetic version of exendin-4, exenatide (Byetta), has been formulated, and has been available as a twice daily injection for the treatment of diabetes since 2005. Subsequently GLP-1 has been manipulated in other ways to prolong its half-life, and three other analogues are now available as diabetes treatments: liraglutide (Victoza) is acetylated GLP-1; exenatide extended release (Bydureon) is exenatide incorporated into microspheres, and the recently licensed albiglutide (Tanzeum) consists of two DPP-4-resistant human GLP-1 sequences fused to recombinant human albumin (Matthews *et al.* 2008).

Another mechanism used to improve hormone activity is targeted amino acid replacement. A synthetic version of amylin, pramlintide (Symlin) has been produced in this way. This has three substituted proline residues, which stops it forming fibrils. It is stable and soluble (Young *et al.* 1996). This has been licensed in the USA as the first new treatment for type 1 diabetes since insulin in the 1920s. Targeted amino acid substitution has been used within our lab to produce gut hormone analogues which have both longer half-lives than the native hormone, and are more potent at causing weight loss. A pancreatic

polypeptide analogue has been through phase 1 clinical trials (Tan *et al.* 2012), and a PYY analogue is undergoing phase 1 trials (ClinicalTrials.gov Identifier: NCT01515319). Both of these caused significant weight loss in pre-clinical trials. Targeted substitutions have also been used to produce oxyntomodulin analogues that are currently in trials by Thiakis/Pfizer and Zealand Pharma.

PEGylation has been used to prolong the half-life of gut hormones. The half-life of native PYY is approximately 8 min within the circulation (Lluis *et al.* 1989). Conventional PEGylation renders PYY relatively inactive by preventing receptor binding (Shechter *et al.* 2005). However, by designing a PEGylated conjugate of PYY(3–36) wherein the PEG molecule was pH sensitive, and would become freed in plasma, Shechter *et al.* produced a PYY-related drug which retained the satiety effects of the native peptide, but with a half-life prolonged to more than 7 h, and functional activity that led to a 30% reduction in food intake even 24 h after administration (Shechter *et al.* 2005). A similar strategy of reversible PEGylation has been applied to oxyntomodulin, where a weekly injection of hormone caused a reduction in food intake of 29%, and a reduction in body weight of 28% over a 30 day period (Herskovitz *et al.* 2013).

	Gastric Band	Restrictive
	Sleeve Gastrectomy	Restrictive
	Jejuno-ileal Bypass	Bypass
	Roux-en-Y Bypass	Bypass and Restrictive

Figure 3. Types of bypass surgery

Stable hormonal formulations are therefore possible. However, this does not guarantee the efficacy of the drug in clinical practice. It is instructive to look at the efficacy of the currently available gut hormone medications at causing weight loss. Licensed for treatment of diabetes, pramlintide and albiglutide effectively reduce glycosylated haemoglobin. However, the weight loss they cause is, in clinical practice, limited. A meta-analysis of pramlintide suggested weight loss of just over 2 kg over up to 6 months (Singh-Franco *et al.* 2011); however, subgroup analysis showed that weight loss at the maximum licensed dose of 120 μg was only 1.8 kg, and that greater weight loss was seen at doses of 150–360 μg (Singh-Franco *et al.* 2011). Following 16 weeks of albiglutide therapy, weight loss in subjects failed to reach statistical significance, ranging between -1.1 and -1.7 kg, compared to -0.7 kg in the control group. Exenatide and liraglutide fare better: meta-analyses of both have shown that they do cause significant weight loss over periods ranging between 4 and 26 weeks, with absolute weight loss of up to 6 kg over the study periods (Norris *et al.* 2009; Niswender *et al.* 2013). However, as with pramlintide, greater degrees of weight loss are seen at higher drug doses, often above those currently licensed. Astrup *et al.* undertook a randomised, double-blind, placebo-controlled, multinational study using liraglutide. After 1 year, those on the maximum licensed dose (1.2 mg daily) had lost an average 3.8 kg, which was non-significant; however, significant weight loss was achieved in those on 1.8 mg or more of liraglutide daily, to a maximum of 7.8 kg weight loss after 1 year in those on 3.0 mg daily of liraglutide. This went up to 10.3 ± 7.1 kg weight loss over 2 years from screening (Astrup *et al.* 2012). As such, the manufacturers of liraglutide, Novo Nordisk, have recently filed with the US Food and Drug Administration (FDA) for high-dose 3 mg liraglutide to be licensed as an obesity therapy.

Effective obesity therapies are often beset with problematic side-effects. All GLP-1 agonists are associated with nausea. More than 50% of subjects receiving 3 mg daily of liraglutide complained of nausea and vomiting, and though in the majority of cases this was mild or moderate, and tended to be transient, 4% did withdraw from the trial because of this (Astrup *et al.* 2012). In the albiglutide trial, more than 50% of subjects experienced nausea at higher doses (Rosenstock *et al.* 2009). Nausea arises from rapid increases in plasma levels of peptides. One strategy to overcome this has been continuous administration of GLP-1 for one year via an implanted minipump; this is so far well tolerated, and is undergoing phase III clinical trials as a treatment for diabetes (Henry *et al.* 2014; www.intarcia.com).

Rapid increases in plasma peptide levels, and the ensuing nausea, have also scuppered development of a PYY therapy. Merck and Natestch Pharmaceutical produced a nasal spray formulation of PYY, hoping to make the route

of administration more acceptable than subcutaneous injections. However, the swift absorption through the nasal membrane led to rapid peaks in plasma levels. Seventy-eight per cent of subjects receiving 600 μg three times a day experienced nausea, and almost 50% of the same group suffered from vomiting, so more than 60% of subjects discontinued therapy at this dose (Gantz *et al.* 2007). Despite these gastrointestinal side-effects, this dose did not produce significant weight loss (Gantz *et al.* 2007). Osmotic mini-pumps have been used to deliver PYY continuously in rodent studies, which could limit peaks in plasma levels and limit nausea; however, these only produce a transient reduction in food intake, suggesting the possibility that tolerance could develop to PYY delivered in this way (Adams *et al.* 2006).

Side-effects have also limited development of CCK-based treatments. CCK, initially known as cholecystokinin-pancreozymin, increases amylase secretion (Banwell *et al.* 1967), and can cause acute pancreatitis (Niederau *et al.* 1986). It also has potential role in the development of pancreatic cancer: CCK causes pancreatic acinar cell proliferation via the MAPK/c-Jun/AP-1 pathway (Guo *et al.* 2012), and can increase cell numbers in certain pancreatic cancer cell lines (Ohlsson *et al.* 1999). Such concerns make development of CCK-based therapies unlikely. Similar concerns about pancreatitis and pancreatic cancer have recently been raised about GLP-1 analogues; however, large-scale reviews by both the FDA and the European Medicines Agency (EMA) have failed to find any firm evidence of such in spite of considerable animal testing and human experience (Egan *et al.* 2014).

All currently available gut hormone preparations require subcutaneous injection, as peptides are digested in the stomach and intestine. A number of groups have nevertheless tried to develop oral formulations. GLP-1 and PYY have been conjugated with vitamin B12, with a view to using the highly effective B12 uptake system in the stomach to facilitate peptide absorption; however, no feeding studies have yet been performed with these peptides (Fazen *et al.* 2011; Clardy-James *et al.* 2013). Another delivery agent, used by Christoph Beglinger's group in Basel, is sodium *N*-[8-(2-hydroxybenzoyl) amino]caprylate, or SNAC. This enhances the lipophilicity of the peptides, enabling them to be transported across the intestinal epithelium. Once in the plasma the delivery molecule and drug dissociate (Beglinger *et al.* 2008). Ingestion of SNAC-GLP-1, or SNAC-GLP-1 in combination with SNAC-PYY, reduce food intake at a test meal in healthy volunteers by up to 20%, though with notable variability between subjects (Steinert *et al.* 2010). Furthermore, a single dose produced no change in food consumption over a 24 h period, and 2 of the 12 subjects suffered gastrointestinal side-effects during co-administration of the peptides (Steinert *et al.* 2010).

As ghrelin works to increase food intake, it has to be targeted in different ways to the above satiety signals. Approaches have included antagonists and inverse agonists at the ghrelin receptor, neutralisation of ghrelin through vaccines or Spiegelmers (single-stranded mirror image oligonucleotides), and through reducing levels of activated ghrelin by targeting the enzyme GOAT. The success of these strategies has been varied. Some ghrelin antagonists reduced body weight in rats by 15% (Esler *et al.* 2007), though others which worked *in vitro* caused an increased body weight *in vivo* (Halem *et al.* 2005). Rats who developed antibodies against their own ghrelin through inoculation with a ghrelin hapten showed reduced body weight gain, though daily food intake did not change (Zorrilla *et al.* 2006), but a vaccine trial in man by Cyto Biotechnology caused no significant weight loss in obese subjects. GOAT inhibitors reduced weight gain in lean mice (Barnett *et al.* 2010), but are unlikely to help in obese subjects as ghrelin levels are already suppressed (Homaee *et al.* 2011). Though the ghrelin system is being targeted in clinical trials to treat other conditions (Alize Pharma have started trials of AZP-531, an unacylated ghrelin analogue, to treat diabetes, and Rhythm has a ghrelin analogue, RM-131, in phase II trials to treat gastroparesis), we are unaware of any clinical trials at present that are targeting the ghrelin system to treat obesity. Since ghrelin is low in obesity it might be that it is autosuppressed and further suppression is ineffective.

Medical bypass

Significant side-effects and modest weight loss mean a single hormone therapy is unlikely to be the solution to the obesity pandemic. Following gastric bypass, it is the increased secretion of multiple gut hormones that appears to be effective. There is also increasing evidence that gut hormones interact and augment each other's effects. Intraperitoneal injections of PYY(3–36) enhanced glucose-stimulated GLP-1 levels within the hepatic portal vein (although systemic GLP-1 levels remained unchanged) (Chandarana *et al.* 2013), while cholecystokinin stimulates isolated neurons that produce GLP-1 within the brain via an increase in glutaminergic synaptic activity (Hisadome *et al.* 2011). Therefore, emulating the success of bariatric surgery means targeting multiple gut hormone pathways simultaneously.

Oxyntomodulin is a naturally occurring dual agonist at the glucagon and GLP-1 receptor and a number of studies have shown that activation of both receptors improves weight loss effects compared to single receptor activation (Pocai *et al.* 2009; Day *et al.* 2009, 2012). Co-administration of two separate native peptides has also been investigated. Neary *et al.* administered very low dose GLP-1 and PYY(3–36) either alone or in combination

to rats; though at these concentrations alone neither hormone reduced food intake, when combined, food intake was significantly reduced for 4 h (Neary *et al.* 2005). A similar pattern was seen following infusion of GLP-1 and PYY(3–36) in human volunteers: GLP-1 at $0.4 \text{ pmol kg}^{-1} \text{ min}^{-1}$ had no significant effect on food intake, while PYY at $0.4 \text{ pmol kg}^{-1} \text{ min}^{-1}$ reduced food intake by 15%; however, when both peptides were infused, food intake at a subsequent buffet meal was reduced by 27%, and also significantly reduced over the following 24 h, without causing increased nausea (Neary *et al.* 2005). Similarly, Shi *et al.* showed that PYY(3–36) and pancreatic polypeptide, administered at anorectic doses (47 nmol kg^{-1} of pancreatic polypeptide and 74 nmol kg^{-1} of PYY), had an additive effect on reducing food intake in mice. However, the synergistic effect of peptides is dose dependent. Thus, at subanorectic doses of PP and PYY (30 nmol kg^{-1} of each peptide), co-administration did not significantly reduce food intake in mice (Neary *et al.* 2008); furthermore, when the two peptides were infused into humans at subanorectic doses, food intake actually increased in the co-administration group compared to either peptide alone (Neary *et al.* 2008).

Single drugs that target multiple gut hormones have been or are in development. A synthetic peptide with properties of both PYY and PP, obinipitide, had been developed by 7TMpharma, and was reported to show promising results in early clinical trials. Development at the moment has been shelved as it was not that effective. An alternative approach includes administering two stable formulations of different peptides together; as such, a single injection containing a PYY analogue and an oxyntomodulin analogue which activates the Y2, GLP-1 and glucagon receptor has been shown to cause significant weight loss in pre-clinical trials, and will soon enter phase I clinical trials (S. R. Bloom, unpublished observations).

Conclusion

Gut hormones have provided a focus in obesity research for more than 40 years. It is now possible to reliably make a fat mouse thin. Under clinical trial conditions, gut hormones can help reduce appetite and cause weight loss in man. Stable peptide preparations are available and in wide clinical use in the treatment of diabetes, and many gut hormone analogues are entering clinical trials and show a great deal of promise. However, at present, there is no simple solution to the obesity pandemic. Gut hormones may provide an effective medical solution in time. Meanwhile, we are beholden to the memory of Bayliss and Starling, and all those people world-wide who suffer from obesity, to persevere within this field until a solution is found.

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Additional information

Competing interests

None declared.

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