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Obesity treatment: novel peripheral targets

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Our knowledge of the complex mechanisms underlying energy homeostasis has expanded enormously in recent years. Food intake and body weight are tightly regulated by the hypothalamus, brainstem and reward circuits, on the basis both of cognitive inputs and of diverse humoral and neuronal signals of nutritional status. Several gut hormones, including cholecystokinin, glucagon-like peptide-1, peptide YY, oxyntomodulin, amylin, pancreatic polypeptide and ghrelin, have been shown to play an important role in regulating short-term food intake. These hormones therefore represent potential targets in the development of novel anti-obesity drugs. This review focuses on the role of gut hormones in short- and long-term regulation of food intake, and on the current state of development of gut hormone-based obesity therapies.

Obesity is classified by the World Health Organization as one of the eight principal causes of preventable chronic disease worldwide [1]. Recent, dramatic increases in its prevalence have resulted in a major burden on healthcare resources in many industrialized countries [2–5]. Obesity substantially increases an individual's risk of cardiovascular disease, stroke, peripheral vascular disease, renal failure, cancer, osteoarthritis and Type 2 diabetes mellitus [6, 7]. Indeed, a prospective cohort study of 114 281 women revealed an exponential relationship between body mass index (BMI) and risk of developing Type 2 diabetes mellitus, with those in the group with highest BMI being 93 times more likely to develop diabetes than those in the lowest group, after 14 years of follow-up [8].

Treatment options for obesity are limited. A combination of dieting and increased physical activity is effective only for as long as it is adhered to, a challenge even for participants in randomized trials [9]. Currently available medications are hampered by significant adverse effects and are only moderately effective, with weight loss persisting only for as long as treatment is continued [10]. In contrast, bariatric surgery routinely results in substantial, permanent weight loss and, despite significant perioperative risks, is the only treatment modality shown to reduce mortality in severe obesity [11, 12].

The two most commonly performed bariatric procedures are gastric banding and Roux-en-Y gastric bypass (RYGB). Unlike gastric banding, a solely restrictive procedure, RYGB combines gastric restriction with diversion of food away from the gastric fundus and proximal small bowel. Although RYGB is therefore a more complicated procedure, it generally produces greater weight loss and more rapid resolution of diabetes than gastric banding [13–15]. It is likely that this superiority results, at least in part, from altered patterns of secretion of several gut hormones, including peptide YY (PYY), glucagon-like peptide-1 (GLP-1) and oxyntomodulin, which occur after RYGB but not after purely restrictive procedures [16–18]. Similar patterns of secretion are observed in previously healthy people who lose weight following small bowel resections [19]. These and other observations have encouraged research into the role of gut hormones in regulating appetite and body weight, and into the possibility that they could represent valuable new targets in the development of anti-obesity medications.

GLP-1

Of all the known gut hormones, GLP-1 has proved to be the most amenable target for drug development to date. One of several cleavage products of the proglucagon precursor, GLP-1 is secreted by L-cells located predominantly in the distal intestine [20]. Release nevertheless occurs rapidly

after eating, in proportion to food intake, under the control of the vagus nerve, enteric nervous system, other circulating gut peptides and the direct effect of nutrients on L-cells [21–25].

GLP-1 acts by binding to the GLP-1 receptor (GLP-1R), a seven *trans*-membrane domain, G-protein-coupled receptor [26]. Ligand binding stimulates adenylate cyclase activity and increases the influx of extracellular Ca^{2+} ions [26, 27]. The GLP-1R is expressed in many tissues, including pancreatic islets, lung, brain, stomach, kidney and heart [26, 28]. The function of GLP-1 in several of these sites is not yet understood. However, in pancreatic islets, it functions as an incretin hormone, i.e. as a physiological, glucose-dependent, insulin secretagogue, the action of which is to potentiate postprandial insulin release [25]. In rodents, GLP-1 also increases β-cell mass [29]. It is a matter of conjecture as to whether a similar process may occur in humans. GLP-1 also inhibits glucagon secretion, delays gastric emptying [30, 31], and inhibits food intake in rats, after administration either systemically or directly into the central nervous system (CNS) [32–34]. In humans, acute intravenous (i.v.) infusion reduces energy intake at a subsequent *ad libitum* meal [35], whereas chronic subcutaneous infusion to patients with Type 2 diabetes mellitus results in weight loss and improved glycaemic control [36].

It is likely that the satiating effect of GLP-1 is due not only to delayed gastric emptying but also to direct effects in the CNS, since peripherally administered GLP-1 causes neuronal activation in the arcuate nucleus [37], whereas administration into the CNS causes neuronal activation in the paraventricular nucleus, nucleus of the tractus solitarius and area postrema [38, 39]. Furthermore, GLP-1R gene expression is altered in the hypothalamus and brainstem by fasting and refeeding [40]. It is also possible that GLP-1 acts via the vagus nerve, since GLP-1R gene expression occurs in the nodose ganglion of the vagus nerve [41], and the effect of peripherally administered GLP-1 on both energy intake and activation of arcuate nucleus neurons is attenuated by either bilateral sub-diaphragmatic truncal vagotomy or bilateral transections of the brainstem–hypothalamus pathway [37].

Recognition of the incretin and satiety-inducing properties of GLP-1 has made it a prime target for the development of treatments for diabetes and obesity. However, GLP-1 is not itself suitable for use as a drug, owing to the rapidity with which it is inactivated and cleared from the circulation, both by the action of dipeptidyl peptidase-IV (DPP-4) and by renal clearance [42–44]. This problem has been circumvented by the development of injectable, DPP-4-resistant incretin mimetics (i.e. GLP-1R agonists) and of orally available DPP-4 inhibitors. Examples of both these classes are currently licensed for the treatment of Type 2 diabetes mellitus. However, in contrast to the incretin mimetics, DPP-4 inhibitors have not consistently caused weight loss in Phase III clinical trials. This may be because DPP-4 does not function solely as an inactivator of GLP-1 but, rather, modifies a multitude of peptides, including cytokines [45].

The first available incretin mimetic is exenatide (Byetta; Amylin/Eli Lilly, Basingstoke, UK), this being the pharmaceutical name for exendin-4, a naturally occurring potent GLP-1R agonist that is resistant to DPP-4-mediated degradation [46, 47]. Exenatide is administered by twice-daily subcutaneous injection for the treatment of Type 2 diabetes mellitus, as an adjunct to metformin and/or sulphonylureas. A long-acting version is in development that could allow once-weekly dosing [48, 49]. Phase III trials of short-acting exenatide in patients with Type 2 diabetes showed not only that it improves glycaemic control but also that it significantly reduces body weight [50–55]. Nausea occurs very commonly, although its incidence declines with duration of treatment [50, 51]. It has been claimed that weight loss during exenatide treatment is not a consequence of nausea [50, 51]. Recent reports have given rise to the concern that exenatide use might increase the risk of developing acute pancreatitis [56, 57]. However, an analysis of health insurance claims in the USA suggests that this risk may in fact be no greater than that for patients started on other antidiabetic medications [58].

It has been hypothesized that exenatide could be used as a treatment for obesity in patients without diabetes. However, although trials are in progress, sparse peer-reviewed data have been published as yet. The exception is a small-scale, open-label study conducted in obese, nondiabetic women with polycystic ovary syndrome. The authors reported that exenatide and metformin in combination had beneficial effects on menstrual cyclicity, rate of ovulation, body weight and insulin sensitivity, and that these effects were more marked than treatment with either exenatide or metformin alone. There were no reported instances of hypoglycaemia [59].

Several other incretin mimetics are in development at present. Liraglutide (Victoza; Novo Nordisk, Crawley, UK) is an analogue of GLP-1(7-37) that received a licence for use in the treatment of Type 2 diabetes mellitus earlier this year. Its half-life is prolonged by albumin binding, which results from the addition of a side chain, comprising a glutamic acid residue coupled to a palmitoyl group, to lysine at position 26 [60]. In human studies, liraglutide has been shown to improve glycaemic control in association with weight loss [61–64]. As with exenatide, the major adverse effect is nausea. There are no published data regarding the effect of liraglutide on body weight in nondiabetic individuals as yet. Other molecules, including taspoglutide (Roche, Welwyn Garden City, UK) and albiglutide (GlaxoSmithKline, Brentford, UK), are at earlier stages of development but may have half-lives sufficient for weekly dosing [65, 66].

Oxyntomodulin

Like GLP-1, oxyntomodulin is released postprandially from intestinal L-cells, in proportion to energy intake [67, 68]. Its actions include inhibition of gastric acid and pancreatic exocrine secretion, and prolongation of gastric emptying [68–73]. When administered to rats by either intracerebroventricular or peripheral injection, oxyntomodulin reduces food intake, increases energy expenditure and reduces the rate of increase in body weight [74–77]. In humans, i.v. infusion of oxyntomodulin reduces food intake [78], while repeated subcutaneous injection increases energy expenditure and causes weight loss in obese volunteers [79, 80].

Oxyntomodulin is another product of tissue-specific cleavage of the proglucagon precursor, comprising the entire 29-amino-acid sequence of glucagon with a C-terminal octapeptide extension [81–83]. It is an agonist at both the glucagon receptor (GLU-R) and the GLP-1R [74], but its anorectic effect is probably mediated via the latter receptor, since co-administration of exendin-(9-39), a specific GLP-1R antagonist, restores food intake to that of controls [74, 75]. Furthermore, whereas the anorectic effect of oxyntomodulin is maintained in mice lacking the GLU-R, it is absent in those lacking the GLP-1R [74].

Although oxyntomodulin is a GLP-1R agonist, several strands of evidence point to it having functions that are distinct from those of GLP-1. First, the affinity of oxyntomodulin for the GLP-1R is about fivefold less than that of GLP-1, yet the two hormones are virtually identical in their anorectic effect in rodents [75]. Second, injection of exendin-(9-39) into the arcuate nucleus prevents oxyntomodulin, but not GLP-1, from reducing food intake after intraperitoneal (i.p.) injection [77]. Third, functional imaging studies using manganese-enhanced magnetic resonance in mice show that oxyntomodulin and GLP-1 differ substantially in their effects on hypothalamic neuronal activity [84, 85]. These findings suggest that there may be an unknown oxyntomodulin-specific receptor, and/or that there may be differences between oxyntomodulin and GLP-1 in regional uptake within the CNS.

Like GLP-1, oxyntomodulin is inactivated by DPP-4 and neprilysin [86, 87] and cleared rapidly from the circulation [79]. This laboratory has used oxyntomodulin analogues to investigate the contribution of different regions of the molecule to its function and its sensitivity to proteolytic degradation [86]. An analogue of oxyntomodulin synthesized as part of this programme was developed by Thiakis and is now being evaluated by Wyeth Pharmaceuticals as a potential therapy for obesity.

Peptide YY

Another product of intestinal L-cells, PYY is co-secreted with GLP-1 and oxyntomodulin after meals, in proportion to the calories consumed, with protein providing a greater stimulus to its release than fat [68, 88–90]. Plasma PYY concentration reaches a peak 1–2 h after each meal [90]. The hormone exists in two major forms in the circulation: PYY_{1-36}, which has agonist activity at the Y_1, Y_2 and Y_5 receptors (Y_1R, Y_2R, Y_5R), and PYY_{3-36}, which is a selective Y_2R agonist [91, 92]. The predominant circulating moiety, PYY_{3-36}, is formed by DPP-4-mediated proteolysis of the full-length peptide [93, 94].

PYY was originally described as being an appetite stimulant because of its potent effect when administered by intracerebroventricular injection [95]. However, autoradiographic studies show that radiolabelled PYY_{3-36} binds only at the area postrema, subfornical organ and median eminence in the CNS after peripheral administration [96]. Thus, the effect of intracerebroventricular PYY is unlikely to be representative of the physiological properties of circulating PYY.

Far from being an appetite stimulant, PYY_{3-36} is now thought to be a satiety-inducing hormone [97]. Several facts suggest that this satiating effect is mediated via Y_2R in the arcuate nucleus. First, food intake in rodents is reduced by injection of PYY_{3-36} directly into the arcuate nucleus [97]. Second, peripheral injection of PYY_{3-36} increases *c-fos* expression, a marker of neuronal activation, in the arcuate nucleus [97]. Third, PYY_{3-36} has no effect on food intake in Y_2R-knockout mice [97]. Fourth, prior administration of a selective Y_2R antagonist, either by intra-arcuate injection [98] or by i.p. injection [99], prevents inhibition of food intake by i.p. PYY_{3-36}.

However, PYY_{3-36} may exert effects on food intake not only at the arcuate nucleus but also via the vagus–brainstem–hypothalamic pathway. The Y_2R is expressed in the nodose ganglion [100] and vagal ligation studies show that Y_2R are transported to the peripheral terminals of vagal afferent neurons [101]. This is reflected in the fact that i.v. PYY_{3-36} causes afferent vagal discharges [101], while disruption of the vagus–brainstem–hypothalamus pathway, either by subdiaphragmatic truncal vagotomy or by bilateral midbrain transections rostral to the nucleus of the tractus solitarius, abolishes the satiating effect of i.p. PYY_{3-36} [37, 101]. Subdiaphragmatic truncal vagotomy also prevents *c-fos* expression in the arcuate nucleus in response to PYY_{3-36} administered by i.p. injection [101].

The first report of the anorectic and weight loss-inducing effects of PYY_{3-36} [97] was questioned by a number of other research groups, who were unable to demonstrate any reduction in food intake, either acute or chronic, in rodents [102, 103]. Since then, further studies in mice, rats, pigs, rhesus monkeys and humans have confirmed the acute anorectic properties of PYY_{3-36} [98, 99, 104–118]. Several studies have also confirmed the ability of chronic PYY_{3-36} administration to cause weight loss in animal models of obesity [119–124]. It is possible that the failure of several groups to replicate the anorectic effects of PYY_{3-36} in rodents was due to inadequate acclimatization

of the animals to study conditions [125]. Nevertheless, an attempt to use intranasally-delivered PYY_{3-36} as a treatment for obesity has foundered after significant problems with nausea and vomiting were encountered during a Phase II clinical trial [126].

Cholecystokinin

Cholecystokinin (CCK) is released postprandially by endocrine I-cells in the small intestine [127, 128]. Several cleavage products of the pro-CCK gene circulate in plasma, the minimal epitope for receptor binding being a carboxy-terminal-amidated, tyrosyl *O*-sulphated heptapeptide [129]. CCK-8, the shortest bioactive form, functions as a neurotransmitter, binding to both CCK1 (also known as CCK-A) and CCK2 (CCK-B) receptors in the CNS [130, 131]. In the gastrointestinal tract, CCK acts via the CCK1 receptor [132, 133] with several effects, including gallbladder contraction, sphincter of Oddi relaxation, pancreatic enzyme release and somatostatin release [134].

Peripheral administration of CCK causes early meal termination in rats, reducing short-term food intake [135]. This satiating effect is abolished by truncal vagotomy or capsaicin-induced afferent fibre ablation, suggesting that it is mediated by the vagus [136–139]. Human food intake may also be reduced acutely by administration of CCK [140–144]. However, early satiety at each meal does not necessarily translate into reduced long-term appetite. Indeed, in a clinical trial of a CCK1 receptor agonist developed by GlaxoSmithKline, mean body weight was similar in placebo- and drug-treated groups after 24 weeks' treatment [145]. This finding is reflected in rodent studies showing that tolerance to a continuous i.p. infusion of CCK develops within 24 h [146], and that reduced meal size during repeated CCK injection is compensated for by increased meal frequency [147]. Nevertheless, daily CCK injections enhance the effect of continuous intracerebroventricular infusion of leptin on body weight in rats [148], possibly by increasing the rate of leptin transport across the blood–brain barrier [149]. Further studies are required to investigate whether co-administration with leptin or other hormones may provide a role for CCK1 receptor agonists in the treatment of human obesity.

Pancreatic polypeptide

Pancreatic polypeptide (PP) shares a hairpin-fold tertiary structure, known as the PP-fold, with PYY and neuropeptide Y [150]. The product of pancreatic islet PP-cells, it is secreted postprandially in proportion to the calorie content of ingested food [151–153]. Secretion is under vagal control, and is reduced by either atropine or vagotomy [154]. PP is a high-affinity agonist at the Y_4 receptor (Y_4R) but is also able to bind to the Y_1R and Y_5R [155]. As with PYY, the effect of exogenous PP on rodent food intake depends on route of administration, with the intracerebroventricular route resulting in an increase in food intake [156–158] but i.p. administration having the opposite effect [156, 159, 160]. Autoradiographic studies show that, after peripheral administration, ^{125}I-labelled PP uptake occurs only in the area postrema, suggesting that the effect of intracerebroventricular PP is unlikely to be physiological [161].

Early animal studies showed that chronic administration of PP by i.p. injection reduces food intake and weight gain in ob/ob mice [160]. In New Zealand obese mice, similar treatment reduces hyperglycaemia, hyperinsulinaemia and weight gain [162]. More recent studies have shown that mice with selective transgenic overexpression of PP in pancreatic islets, resulting in a 20-fold increase in plasma PP concentration, are lean and hypophagic in comparison with controls [163]. Furthermore, this phenotype is reversed by administration of anti-PP antiserum [163]. Indirect calorimetry has been used to show that weight loss in ob/ob mice receiving PP is likely to occur both through a reduction in food intake and also through an increase in energy expenditure [159].

The effect of PP on human food intake was first studied in children with Prader-Willi syndrome, following the observation that meal-stimulated PP secretion is attenuated in this condition [164, 165]. In an initial study, i.v. infusion of extracted bovine PP did not affect measured food intake, but several parents noticed that their children had eaten less than usual after returning home from study infusions [166]. A second study was therefore performed, with a more prolonged infusion protocol, resulting in a 12% decrease in food intake [167]. More recently, human sequence PP has also been shown to reduce food intake in lean human volunteers [168, 169], and to delay gastric emptying [170]. However, since PP is degraded rapidly in the circulation [171], it is likely that its use as a treatment for obesity will depend on the development of long-acting Y_4R agonists.

Amylin

Amylin is co-secreted with insulin by pancreatic islet β-cells and binds to a receptor complex that comprises the calcitonin receptor coupled to receptor activity-modifying proteins [172–176]. Peripheral administration of amylin in rats retards gastric emptying [177] and reduces food intake [178]. The anorectic effect is probably mediated via the area postrema, since it is abolished by experimental lesions in this area [179]. Furthermore, neuronal activation in the area postrema may be demonstrated by *c-fos* immunocytochemistry after peripheral administration of amylin [180].

A stable analogue of amylin, named pramlintide (Symlin; Amylin Pharmaceuticals, San Diego, CA, USA), is

licensed in the USA for use as an adjunct to insulin treatment in both Type 1 and Type 2 diabetes mellitus, and its use in patients with these diseases is associated with modest weight loss [181–184]. In addition, small-scale trials of its efficacy as an obesity treatment have demonstrated that it may also be of use in patients without diabetes, both as monotherapy and in combination with a leptin receptor agonist [185, 186].

Ghrelin

Ghrelin is an octanoylated peptide, secreted by endocrine cells in the gastric fundus, that activates the growth hormone secretagogue receptor (GHS-R1a) [187, 188]. In contrast to other gut hormones, it is a potent orexigenic agent, causing hyperphagia after acute administration in humans [189, 190] and weight gain during repeated administration to rodents [191, 192]. Furthermore, chronic treatment with an orally available GHS-R1a agonist causes weight gain in humans [193].

Despite the negative correlation between ghrelin levels and BMI, a study of the effect of ghrelin infusion on acute food intake has shown that obese individuals may be more sensitive to the orexigenic effects of ghrelin than lean individuals [190]. In addition, obesity is associated with attenuation of the usual postprandial fall in ghrelin levels [194]. Furthermore, the GHS-R1a exhibits constitutive activity, suggesting that an inverse agonist may have greater anorectic effect than an antagonist [195]. These factors suggest that disruption of ghrelin signalling may prove useful for treating obesity.

Various approaches have been used to block ghrelin activity, including GHS-R1a antagonists [196, 197], RNA Spiegelmers [198–200], anti-ghrelin vaccines [201, 202] and use of somatostatin to inhibit endogenous ghrelin release [203–205]. A number of orally available GHS-R1a antagonists have also been developed, the most promising of which have been shown in rodents to cause reductions in food intake and body weight and to improve glucose tolerance [206, 207]. However, a viable treatment for human obesity has yet to emerge from any of these strategies.

Conclusions

Satiety in humans is experienced as a spectrum that ranges from extreme hunger at one end, through the onset of satiation during a meal, to feelings of fullness and then nausea at the other end. Gut hormones play an important role in generating satiety, alongside neuronal afferent pathways and blood-borne humoral and nutrient signals. However, clinical trial experience has shown that enhanced satiety alone may not be sufficient to cause weight loss during chronic treatment [145]. Put another way, using gut hormone-based treatment to advance the onset of satiety at each meal may not necessarily lead to alterations in either long-term food intake or energy expenditure. Thus one of the major challenges in this field is to improve understanding of the physiological role of each gut hormone, integrating this knowledge into a comprehensive model of energy homeostasis.

As new peripheral targets for anti-obesity drug development, gut hormones also pose several other challenges. Amongst the greatest of these are that the native hormones are not orally available, and that they are cleared rapidly from the circulation, rendering their use by subcutaneous infusion or injection uneconomic. Various approaches have been proposed to circumvent these issues, including the use of other routes of administration, e.g. intranasal, inhalational or transdermal, the modification of peptide structures to render them resistant to proteolysis and clearance, and the synthesis of small molecule agonists. Each approach has its merits, but success may be most likely when the resulting treatment has a smooth pharmacokinetic profile, reducing the risk of nausea that may occur at high plasma concentrations.

Nausea has proved to be a very common adverse effect of treatment with exenatide, and it also occurs during administration of liraglutide, oxyntomodulin, pramlintide, CCK and PYY_{3-36}. Studies in human volunteers of the anorectic effects of infusions of CCK-8 and PYY_{3-36} suggest that the presence or absence of nausea does not influence the extent of reduction of food intake [113, 208]. Furthermore, there is some evidence that the extent of weight loss with exenatide treatment is not related to the incidence of nausea [50, 51]. Although these findings suggest that maximal anorectic effects may be achieved without inducing nausea, it also seems likely that therapeutic windows may be narrow.

After RYGB, the physiological secretion of several hormones, including GLP-1, oxyntomodulin and PYY_{3-36}, is increased. Although nausea is common in patients who have undergone RYGB, it tends only to occur postprandially, and is rarely severe enough to warrant reversal of the procedure. This gives rise to the hypothesis that treatment with multiple gut hormones could be better tolerated, and more effective, than single hormone treatment. Support for this hypothesis is available from small-scale studies of acute food intake in rodents and humans [99, 116], although not all combinations have proven effective [209, 210]. However, if nausea occurs not simply as a result of excessive satiety but also as a specific, independent side effect, it might be avoided, and weight loss maximized, by co-administration of non-nauseating doses of several hormones.

In summary, gut hormones present many opportunities for anti-obesity drug development. As peripheral targets, they may have relatively few nonspecific side effects compared with centrally acting drugs. Furthermore, it may be possible in the future, through judicious use of combination treatment, to mimic the physiological effect

of RYGB and hence to cause a similar degree of weight loss without the perioperative risk. An ambitious goal? Yes, but one worth striving for.

Competing interests

B.C.T.F. and O.B.C. have no financial interests to declare. S.R.B. is an inventor of United Kingdom patent application nos. PCT/GB02/04082 and PCT/GB/04/00017 and is a consultant for Thiakis, a subsidiary of Wyeth Pharmaceuticals.

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