PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

*Phil. Trans. R. Soc. B* (2006) **361**, 1187–1209
doi:10.1098/rstb.2006.1856
*Published online* 15 June 2006

# Gastrointestinal hormones regulating appetite

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The role of gastrointestinal hormones in the regulation of appetite is reviewed. The gastrointestinal tract is the largest endocrine organ in the body. Gut hormones function to optimize the process of digestion and absorption of nutrients by the gut. In this capacity, their local effects on gastrointestinal motility and secretion have been well characterized. By altering the rate at which nutrients are delivered to compartments of the alimentary canal, the control of food intake arguably constitutes another point at which intervention may promote efficient digestion and nutrient uptake. In recent decades, gut hormones have come to occupy a central place in the complex neuroendocrine interactions that underlie the regulation of energy balance.

Many gut peptides have been shown to influence energy intake. The most well studied in this regard are cholecystokinin (CCK), pancreatic polypeptide, peptide YY, glucagon-like peptide-1 (GLP-1), oxyntomodulin and ghrelin. With the exception of ghrelin, these hormones act to increase satiety and decrease food intake. The mechanisms by which gut hormones modify feeding are the subject of ongoing investigation.

Local effects such as the inhibition of gastric emptying might contribute to the decrease in energy intake. Activation of mechanoreceptors as a result of gastric distension may inhibit further food intake via neural reflex arcs. Circulating gut hormones have also been shown to act directly on neurons in hypothalamic and brainstem centres of appetite control. The median eminence and area postrema are characterized by a deficiency of the blood–brain barrier. Some investigators argue that this renders neighbouring structures, such as the arcuate nucleus of the hypothalamus and the nucleus of the tractus solitarius in the brainstem, susceptible to influence by circulating factors. Extensive reciprocal connections exist between these areas and the hypothalamic paraventricular nucleus and other energy-regulating centres of the central nervous system. In this way, hormonal signals from the gut may be translated into the subjective sensation of satiety. Moreover, the importance of the brain–gut axis in the control of food intake is reflected in the dual role exhibited by many gut peptides as both hormones and neurotransmitters. Peptides such as CCK and GLP-1 are expressed in neurons projecting both into and out of areas of the central nervous system critical to energy balance.

The global increase in the incidence of obesity and the associated burden of morbidity has imparted greater urgency to understanding the processes of appetite control. Appetite regulation offers an integrated model of a brain–gut axis comprising both endocrine and neurological systems. As physiological mediators of satiety, gut hormones offer an attractive therapeutic target in the treatment of obesity.

**Keywords:** pancreatic polypeptide; peptide YY; ghrelin; glucagon-like peptide 1; oxyntomodulin; cholecystokinin

## 1. INTRODUCTION

It was with the discovery of gut hormones a century ago that the field of endocrinology was born. It is therefore fitting that in the last decade or so, gut peptides have taken on an increasingly central role in one of the most pressing public health problems facing the world today, namely that of obesity. The brain–gut axis provides a means by which the gastrointestinal tract signals energy status to the brain. In this review, we shall describe the key part played by gastrointestinal hormones in regulating energy intake.

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One contribution of 16 to a Theme Issue 'Appetite'.

## 2. HISTORICAL PERSPECTIVES

For centuries, Western medical thought was dominated by the doctrine of the humours, and the gut, in particular, was accorded a central role. However, it was not until the early twentieth century that the notion of circulating regulators of gut function was set onto a more sound experimental footing with the work of Bayliss & Starling (1902). They demonstrated that infusion of an acidic solution into a denervated loop of jejunum stimulated pancreatic secretion, whereas intravenous acid did not. Moreover, intravenous injection of an extract of duodenal mucosa reproduced this effect. The putative agent responsible was named 'secretin' and conferred upon its discoverers the distinction of founding a novel branch of physiology. The advent of the 1960s saw the application of a



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Table 1. Overview of the major gut hormones. (CCK, cholecystokinin; CNS, central nervous system; GH, growth hormone; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 and -2, glucagon-like peptides-1 and -2; GRP, gastrin-releasing polypeptide; ICV, intracerebroventricular; PHI, peptide histidine isoleucine; PHV, peptide histidine valine; PP, pancreatic polypeptide; PYY, peptide YY; OXM, oxyntomodulin.)

| peptide | primary sites of synthesis | major actions | important references |
|---|---|---|---|
| CCK | I-cells of duodenum, jejunum; widespread CNS expression | promotes gallbladder contraction<br>increases secretion of pancreatic enzymes and bicarbonate<br>inhibits gastric acid secretion<br>slows gastric emptying<br>reduces food intake | Gibbs *et al.* (1973), Kissileff *et al.* (1981) |
| gastrin | G-cells of gastric antrum | increases gastric acid<br>promotes gastric epithelial cell proliferation<br>no known effect on food intake | Conover *et al.* (1989) |
| ghrelin | A-cells of gastric fundus; small and large intestine; hypothalamic nuclei | promotes release of GH and other pituitary hormones<br>increases food intake<br>promotes gastric motility<br>promotes PP release<br>inotropic effect on heart<br>vasodilatation | Tschop *et al.* (2000), Wren *et al.* (2001*a*) |
| GIP | K-cells of duodenum and jejunum | incretin effect on insulin secretion<br>increases fatty acid synthesis in adipose tissue<br>enterogastrone effect<br>diminishes intestinal motility<br>increases mesenteric blood flow<br>effects on food intake unknown—fourth ventricle administration has no effect | Woods *et al.* (1981), Meier *et al.* (2002), Holst (2004) |
| GLP-1 | L-cells of distal small and large intestine; immunoreactivity in hypothalamus, dorsovagal complex, pituitary | incretin effect on insulin secretion<br>suppresses glucagon release<br>promotes pancreatic β-cell growth<br>inhibits gastric emptying<br>inhibits gastric secretion<br>inhibits energy intake<br>effects on cardiovascular system | Turton *et al.* (1996), Meeran *et al.* (1999), Edwards *et al.* (2001), Tang-Christensen *et al.* (2001), Verdich *et al.* (2001*a*), Baggio *et al.* (2004) |
| GLP-2 | L-cells of distal small and large intestine; immunoreactivity in hypothalamus, dorsovagal complex, pituitary | promotes tissue repair and intestinal mucosal growth<br>enhances digestive and absorptive capacities of intestine<br>inhibits gastric secretion<br>inhibits feeding when administered centrally; no effect of peripheral administration | Tang-Christensen *et al.* (2000), Schmidt *et al.* (2003) |
| motilin | proximal small intestine; some reports of immunoreactivity in CNS | prokinetic action on gut, mediates migrating motor complexes<br>stimulates gallbladder contraction<br>promotes enzyme secretion in stomach and pancreas<br>stimulates PP release<br>effects on food intake equivocal | Olson *et al.* (1980), Garthwaite (1985), Asakawa *et al.* (1998) |
| oxyntomodulin | L-cells of distal small and large intestine; immunoreactivity in hypothalamus, dorsovagal complex, pituitary | inhibits gastric acid production<br>reduces gastric motility<br>role as incretin equivocal<br>inhibits food intake | Dakin *et al.* (2001), Dakin *et al.* (2002), Cohen *et al.* (2003), Wynne *et al.* (2005*b*) |
| PHI/PHV | gastrointestinal tract; heart; lungs; kidney; central and peripheral nervous systems | main physiological effects unclear<br>PHI-injected ICV inhibits feeding | Olszewski *et al.* (2003) |
| PP | pancreatic islets of Langerhans; some reports of expression in hypothalamus, pineal gland, pituitary, substantia nigra, hippocampus | relaxation of gallbladder<br>inhibition of pancreatic exocrine secretion<br>equivocal effect on gastric emptying<br>inhibits food intake | Batterham *et al.* (2003*b*) |
| PYY3-36 | L-cells of distal small and large intestine; immunoreactivity in hypothalamus, medulla, pons | inhibits food intake<br>inhibits gallbladder secretion<br>reduces gut motility<br>inhibits pancreatic secretion<br>enterogastrone effect | Batterham *et al.* (2002), Batterham *et al.* (2003*a*) |

(*Continued*.)

Table 1. (*Continued.*)

| peptide | primary sites of synthesis | major actions | important references |
|---|---|---|---|
| secretin | S-cells of the duodenum | stimulates pancreatic exocrine secretions<br>inhibits gastric secretion<br>promotes PP secretion<br>no known effect on food intake | Conover *et al.* (1989) |
| somatostatin | multiple organ systems, notably the D-cells of the gut and pancreas; hypothalamus | multiple actions across numerous organ systems<br>inhibits gastric secretions<br>reduces gut motility<br>inhibits release of numerous other gut hormones, including insulin, glucagon, CCK, gastrin, OXM, PP<br>reduces food intake when administered peripherally—physiological importance of this effect unclear | Lotter *et al.* (1981), Levine & Morley (1982), Morley *et al.* (1983) |

number of novel techniques to the field and rapid progress flowed from the successive isolation, purification and measurement in the plasma of secretin, gastrin and other gut hormones (Lin & Chey 2003; Dockray 2004; Rehfeld 2004).

The gastro-entero-pancreatic system is now regarded as the largest endocrine organ in the body, and the range of identified hormones secreted by the gut is extensive (see table 1). The primary function of the gut is, of course, the digestion and absorption of nutrients. The gut neuroendocrine system, and at a higher level, the brain–gut axis, functions to optimize this process. The regulation of appetite, and therefore the regulation of the delivery of nutrients to various gut compartments, may be regarded as another facet of this. Many gut hormones therefore alter food intake directly and indirectly, the majority acting to reduce food intake and limit meal size.

## 3. CENTRAL NERVOUS SYSTEM APPETITE CIRCUITS

It is now recognized that these peptides act as true endocrine hormones and exert effects at distant target organs. In particular, in the context of food intake, many gut hormones act on hypothalamic and brainstem centres of appetite control. This provides one means by which the gut may signal energy status to the seat of satiety, the central nervous system (CNS). These CNS neuronal circuits are reviewed in greater detail elsewhere in this issue, but, briefly, the arcuate nucleus (ARC) acts as the site of integration of a number of neurological and blood-borne signals, due to its privileged location near the median eminence. This latter region lacks a complete blood–brain barrier (Peruzzo *et al.* 2000), and therefore some investigators have argued that the ARC is rendered susceptible to influence by circulating factors (Cone *et al.* 2001). Circulating factors modify the activity of two populations of neuron within the ARC. One population co-expresses cocaine- and amphetamine-related transcript (CART) and proopiomelanocortin (POMC) and inhibits food intake. Among the products of cleavage of POMC is α-melanocyte-stimulating hormone, which is a ligand for the melanocortin-4 receptor. The importance of the melanocortin system in the mediation of food intake is illustrated by the observation that up to 6% of monogenetic obesity in humans results from defects in the melanocortin-4 receptor. The second population of neurons increases food intake and co-expresses neuropeptide Y (NPY) and agouti-related protein (Cone *et al.* 2001; Ellacott & Cone 2004; Farooqi & O'Rahilly 2005). Both populations project to the paraventricular nucleus (PVN) and other areas important in the regulation of food intake (figure 1; Schwartz *et al.* 2000).

Extensive reciprocal connections exist between the hypothalamus and the brainstem, particularly the nucleus of the tractus solitarius (NTS; van der Kooy *et al.* 1984; Ter Horst *et al.* 1989). Like the ARC, the brainstem is well placed to receive signals from the blood due to its proximity to other regions with an incomplete blood–brain barrier, e.g. the area postrema. In addition, the brainstem receives vagal afferent neurons from the gastrointestinal tract, and therefore acts as another site of integration between endocrine and neuronal signals.

## 4. CHOLECYSTOKININ

The first gut peptide to be implicated in the control of appetite was cholecystokinin (CCK). CCK is derived from a 115-amino acid precursor, pro-CCK, and selective cleavage gives rise to a number of bioactive forms (Rehfeld 2004). Biological activity resides in the amidated C-terminus of the peptide and all the active species of CCK share a C-terminal heptapeptide sequence that also includes an O-sulphated tyrosine. The major circulating forms in man are CCK-58, -33, -22 and -8 (Rehfeld *et al.* 2001). Non-sulphated forms of CCK also exist, but they constitute minor species of peptide and their biological role remains unclear.

CCK is synthesized in a number of tissues in humans, including the I-cells of the small intestine (Buffa *et al.* 1976), from where it is rapidly released into the circulation in response to a meal (Liddle *et al.* 1985). The basal plasma concentration of CCK is approximately 1 pM, and levels rise to 5–8 pM postprandially (Liddle *et al.* 1985), although many assays for CCK also detect fragments of the peptide.

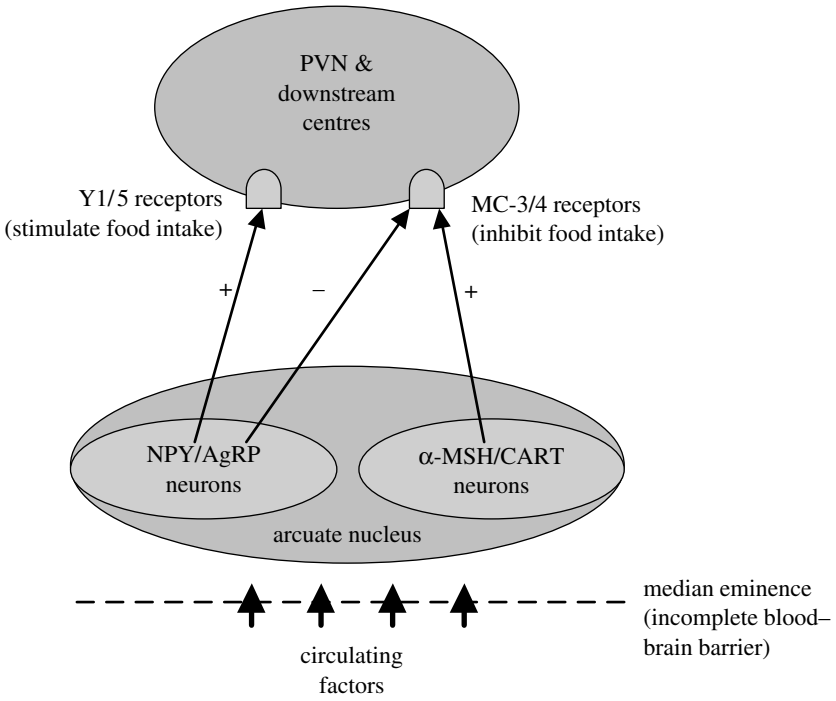


Figure 1. Schematic of the two main appetite-regulating populations of neurons in the hypothalamic arcuate nucleus. α-MSH, α-melanocyte-stimulating hormone (product of proopiomelanocortin cleavage); AgRP, agouti-related protein; CART, cocaine- and amphetamine-related transcript; MC-3/4, melanocortin-3 and -4 receptors; NPY, neuropeptide Y; PVN, paraventricular nucleus; + denotes stimulation of a receptor; − denotes inhibition.

Whether all the CCK measured in plasma is bioactive remains to be established. The concentration of CCK in the circulation remains elevated for up to 5 hours after a meal, and dietary fat and protein, or the products of their digestion, are more potent stimulators of CCK release than carbohydrate (Liddle *et al.* 1985).

CCK also has a dual role as a neurotransmitter, in both the enteric and CNSs (Barden *et al.* 1981; Hutchison *et al.* 1981). The post-translational modification of CCK is tissue-specific, with CCK-8 the predominant form in nervous tissue, whereas longer species are preferentially synthesized in the endocrine cells of the gut (Rehfeld *et al.* 2003).

Two G-protein-coupled receptors for CCK have been identified and may be distinguished by their characteristic pharmacological profiles (Wank 1995). Previously known as the CCK-A and gastrin/CCK-B receptors, they are now designated the CCK-1 and CCK-2 receptors, respectively. Both receptor subtypes are distributed throughout the CNS and gut, although CCK-1 receptors predominate in the alimentary tract, and CCK-2 receptors in the brain (Wank 1995).

CCK acts to cause gallbladder contraction, relaxation of the sphincter of Oddi, stimulation of somatostatin release (and thus inhibition of gastric acid secretion) and stimulation of pancreatic growth and enzyme release via the CCK-1 receptor (Wank 1995). The CCK-2 receptor has been implicated in schizophrenic and anxiety states, and other CNS actions of CCK (Wank 1995; Zachrisson *et al.* 1999; Miyasaka *et al.* 2002). Inevitably, however, the overlap in distribution is reflected in an overlap in function (Morisset *et al.* 2000; Sanjuan *et al.* 2004; Jang *et al.* 2005). Moreover, the hormone gastrin is structurally related to CCK, and its actions on the gastric mucosa are mediated via the CCK-2 receptor, which also binds gastrin with high affinity (Dockray *et al.* 2001).

In addition to those effects summarized above, CCK also alters appetite. Gibbs *et al.* (1973) first demonstrated a dose-dependent effect of exogenous CCK in reducing food intake in rats. This effect occurred without evidence of toxicity and was specific to food intake, CCK having no effect on water intake in water-deprived rats. This finding was subsequently confirmed in humans, in whom an intravenous infusion of the terminal octapeptide of CCK reduced meal size and duration (Kissileff *et al.* 1981). This effect of CCK is short-lived. When administered more than 30 minutes prior to the start of a meal, CCK did not alter food intake (Gibbs *et al.* 1973).

The mechanism by which CCK might exert this effect on appetite is still a matter of ongoing debate. It has been proposed that the inhibitory effect of CCK on gastrointestinal motility, and, in particular, its inhibition of gastric emptying, might be contributory to its inhibitory actions on feeding. Some authors have suggested that in this way, CCK may promote stimulation of gastric mechanoreceptors, and thus invoke neural feedback from the gut to appetite centres in the brain. In support of this hypothesis, low doses of CCK reduced food intake in rhesus monkeys only after a gastric preload of saline (Moran & McHugh 1982). Similarly, in humans, gastric distension was found to augment the reduction of nutrient intake effected by intravenous CCK-8 (Kissileff *et al.* 2003). The use of antagonists to the serotonin receptor subtype 3 ($5\text{-HT}_3$) has recently pointed towards a role for serotonin in the mediation of this effect (Hayes *et al.* 2004).

However, CCK also alters food intake through other pathways that are independent of its effects on the stomach (Moran & McHugh 1988). While the induction of satiety at higher doses of CCK may be attenuated by surgical removal of the pyloric sphincter, lower doses continue to be effective in inhibiting food intake. Lesioning of the vagus nerve abolishes the effects of CCK at the lower doses of the dose–response curve (Moran & Kinzig 2004). The induction of satiety by CCK at physiological concentrations may therefore rely crucially on direct activation of vagal afferent fibres. Others, however, argue that our notion of 'physiological levels' of CCK has been inaccurate in the past due to deficiencies in the assays used, and that the reduction of food intake seen with CCK is pharmacological rather than physiological (Lieverse *et al.* 1993; Baldwin *et al.* 1998; Rehfeld 1998).

CCK-1 receptors are present on afferent fibres of the vagus nerve, and also in the brainstem and dorsomedial nucleus of the hypothalamus (DMH). The use of specific CCK-1 and CCK-2 receptor antagonists has implicated the CCK-1 receptor in the reduction of food intake by CCK (Moran *et al.* 1992). Chronic administration of CCK-1 receptor antagonists or anti-CCK antibodies accelerates weight gain in rodents, though without significant hyperphagia (McLaughlin *et al.* 1985; Meereis-Schwanke *et al.* 1998). The Otsuka–Long–Evans–Tokushima Fatty (OLETF) rat, which lacks CCK-1 receptors, is both hyperphagic and obese (Moran *et al.* 1998; Schwartz *et al.* 1999). Peripherally administered CCK induces *c-fos*, a marker of neuronal activity, in the brainstem (Zittel *et al.* 1999), and food intake in rats is also reduced following direct injection of CCK into a number of hypothalamic nuclei (Blevins *et al.* 2000). Work in OLETF rats has implicated the orexigenic peptide NPY in the mediation of the effects of CCK in the DMH (Bi *et al.* 2001). Thus, the anorectic effects of CCK appear to be mediated by a number of mechanisms, both direct and indirect.

The usefulness of CCK as a therapeutic target in the treatment of obesity, however, may be limited by the short-lived nature of its effects on appetite. Repeated administration does not alter body weight in rats, for although food intake is reduced, meal frequency increases, and so overall intake is unchanged (West *et al.* 1984, 1987*a*,*b*). When given to rats as a continuous intraperitoneal infusion, the anorectic effect of CCK is lost after 24 hours (Crawley & Beinfeld 1983) and Glaxo-Smithkline recently halted trials of its CCK-1 receptor antagonist 181771 after the results made it commercially non-viable (Fong 2005). From the point of view of body weight regulation, CCK may play more of an indirect role in its interaction with signals of longer-term energy balance, such as leptin (Matson *et al.* 2000; Morton *et al.* 2005). The therapeutic potential of this relationship remains to be determined and the physiological or pharmacological nature of the actions of CCK on food intake also awaits further clarification.

## 5. POLYPEPTIDE-FOLD PROTEINS

The polypeptide-fold (PP) family of proteins consists of NPY and two peptides of the gastrointestinal–pancreatic endocrine system, pancreatic PP and peptide YY (PYY). Members of this family of peptides are 36 amino acids in length (with the exception of chicken PYY, which contains 37 amino acids) and undergo C-terminal amidation as a necessary requirement for biological activity. All share a common tertiary structure consisting of a type II proline helix and α-helix connected by a β turn. This structural motif is known as the PP-fold (Fuhlendorff *et al.* 1990). Of this group of peptides, NPY shows the greatest conservation across species, and PP the least (Conlon 2002).

### (a) *Receptors*

Five receptors for the PP-fold family of peptides have been cloned in mammals thus far. Named Y1, Y2, Y4, Y5 and y6 (Michel *et al.* 1998), the y6 receptor is truncated and non-functional in man. All are coupled to inhibitory G-proteins (Gi), and therefore mediate an inhibition of intracellular cyclic-adenosine monophosphate (cAMP) synthesis (Mullins *et al.* 2002). However, they also exhibit a degree of heterogeneity in their coupling to other intracellular signalling pathways. Mullins *et al.* (2002), for instance, showed that while blockade of the protein kinase C pathway completely abolished the effects of Y5 receptor activation, it only diminished the downstream effects mediated by the receptors Y1, Y2 and Y4.

The receptors are diverse in their distribution and this is reviewed in detail elsewhere (Berglund *et al.* 2003). Of particular note in the context of appetite regulation is the mainly presynaptic location of the Y2 receptor subtype in the hypothalamus and elsewhere. Here, it acts as an autoreceptor and inhibits further neurotransmitter release (Smith-White *et al.* 2001). The receptors are classified according to their affinity for different ligands. PYY binds with high affinity to all five receptor subtypes, but the cleavage product PYY3-36 shows selectivity for Y2 and Y5 receptors (see table 2). This diversity in ligand affinity coupled with the differing distributions of the five receptor subtypes ensures that there is scope for this family of peptides to mediate a wide range of biological effects.

### (b) *Peptide YY*

PYY was first isolated from porcine intestine using a technique for the assay of C-terminal amidated peptides (Tatemoto 1982). It is secreted by the L-cells of the gastrointestinal tract, and is widely expressed throughout the gut. Levels of PYY immunoreactivity are low in the proximal small intestine, but increase in the ileum, and continue to rise in the large intestine towards the rectum (Adrian *et al.* 1985*a*). PYY immunoreactivity has also been identified in the human adrenal medulla (Ekblad & Sundler 2002) and in areas of the CNS of the rat, including the hypothalamus, medulla, pons and spinal cord (Ekman *et al.* 1986).

#### (i) *General physiology*

PYY is released into the circulation in response to a meal in proportion to the calories ingested and in

Table 2. Summary of agonist affinities of Y-family receptor subtypes. (NPY, neuropeptide Y; PP, pancreatic polypeptide; PYY, peptide YY (see also Berglund *et al.* 2003).)

| receptor | high-affinity agonists | intermediate-affinity agonists | low-affinity agonists |
|---|---|---|---|
| Y1 | NPY, PYY, $Leu^{31}$,$Pro^{34}$NPY/PYY | NPY2-36, NPY3-36, NPY13-36 | PP |
| Y2 (presynaptic) | NPY, PYY, PYY3-36 | $Leu^{31}$,$Pro^{34}$NPY/PYY | PP |
| Y4 | PP, NPY, PYY, $Leu^{31}$,$Pro^{34}$NPY/PYY | NPY2-36 | NPY/PYY fragments PYY3-36 |
| Y5 | NPY, PYY, NPY2-36, NPY3-36, PYY3-36, $Leu^{31}$,$Pro^{34}$NPY/PYY | PP, NPY13-36, PYY13-36 | NPY/PYY fragments |
| y6 | non-functional in man | | |

relation to the meal composition (Adrian *et al.* 1985*a*). Higher plasma levels of PYY are seen following isocaloric meals of fat compared with meals consisting of protein or carbohydrate. PYY has been invoked as contributing to the 'ileal brake' effect, acting to inhibit further food intake once nutrients have reached the distal small intestine. Interestingly, however, PYY release has been shown to be similar whether intraluminal fat is confined to the proximal or distal half of the small intestine. The release of PYY in response to fat in the proximal small intestine is atropine-sensitive, raising the possibility that a neural reflex (likely involving the vagus nerve) may also mediate PYY release (Fu-Cheng *et al.* 1997; Lin & Chey 2003; Lin & Taylor 2004). Other stimulants of PYY release include intraluminal bile acids, gastric acid and CCK (Onaga *et al.* 2002).

Studies of the actions of PYY initially focused on its local effects within the alimentary tract. At doses of 0.2 pmol $kg^{-1}$ $min^{-1}$ and above, PYY infused into healthy volunteers caused a significant suppression of pentagastrin-stimulated gastric secretions (Adrian *et al.* 1985*b*). It delays gastric emptying (Allen *et al.* 1984; Moran *et al.* 2005) and has an inhibitory effect on gallbladder emptying, an effect probably mediated by the vagus nerve (Hoentjen *et al.* 2001). In common with other hormones of the gastrointestinal tract, PYY also exhibits mitogenic properties, which has led to interest in its effects in pathological states, such as acute pancreatitis (Kazanjian *et al.* 2003).

(ii) *Appetite control: PYY injected into the CNS*

Similarly, the role of PYY in the regulation of appetite and food intake continues to be debated. Initial experiments, in which PYY was administered into the lateral ventricle in rats, suggested the peptide to be a mediator of orexigenic behaviour (Morley *et al.* 1985). Other studies subsequently also found that PYY administered into the CNS increased food intake in rodents (Clark *et al.* 1987; Corp *et al.* 1990, 2001). Observations have also been made of differences in levels of PYY in the cerebrospinal fluid (CSF) of abstaining patients with bulimia nervosa, compared with the same patients shortly after binge eating and vomiting, or compared with healthy controls and patients with anorexia nervosa (Berrettini *et al.* 1988). This has led some researchers to speculate on the place of PYY, acting as a neurotransmitter, in the aetiology of eating disorders. Others, however, point to normalization of these differences in the context of long-term remission as indicative that changes in CSF PYY concentration are a consequence of eating disorders, rather than a cause (Gendall *et al.* 1999).

Matters are complicated by the existence of two species of PYY and multiple receptors (see table 2). As well as the full-length peptide, a truncated form, PYY3-36, is created by cleavage of the N-terminal residues by dipeptidyl peptidase IV (DPP-IV; Eberlein *et al.* 1989; Grandt *et al.* 1994). As described above, PYY3-36 demonstrates relative specificity for the Y2 receptor. When injected into the cerebroventricular system, PYY3-36 also mediates an increase in food intake (Kanatani *et al.* 2000). This effect is attenuated in Y1 and Y5 knockout mice. Injection directly into the ARC, however, inhibits feeding in rodents (Batterham *et al.* 2002). The inhibitory Y2 autoreceptor is highly expressed on orexigenic NPY neurons in the ARC (Broberger *et al.* 1997), whereas Y1 and Y5 receptors are distributed in areas such as the PVN. It has therefore been suggested that the orexigenic effects of ICV-administered PYY and PYY3-36 are mediated by action at Y1 and Y5 receptors. The ARC, however, is associated with a relative deficiency of blood–brain barrier, and is therefore more exposed to circulating PYY3-36 than other appetite regulatory areas of the hypothalamus. Fasting results in an increase in NPY message and peptide expression in the ARC, and it has been proposed that circulating PYY3-36 acts on Y2 receptors in the ARC to reduce NPY expression and thus also reduce food intake. An understanding of the differential distribution of Y-type receptors, and their relative affinities for ligands of the PP-fold family of peptides, is therefore crucial to fully understanding the mechanisms underlying gut hormone regulation of feeding.

(iii) *Appetite control: peripheral injection*

Batterham *et al.* (2002) administered intraperitoneal (IP) injections of PYY3-36 to rats and demonstrated a reduction of food intake in fasted rats, and in non-fasted rats freely feeding during the dark phase (again, when NPY levels in the ARC are high), without a detectable effect on gastric emptying. The dose of PYY3-36 sufficient to bring about this inhibition of feeding resulted in peak plasma levels 15 minutes post-injection that were comparable with physiological postprandial levels of PYY3-36 and resulted in significant induction of *c-fos* expression in the ARC.

Incubation of hypothalamic explants *in vitro* with PYY3-36 resulted in a decrease in NPY release and an increase in α-MSH secretion, and IP injection of PYY3-36 to rats significantly decreased hypothalamic NPY mRNA expression and non-significantly increased POMC mRNA expression (Batterham *et al.* 2002). More recent evidence from studies in which POMC and melanocortin-4 receptor knockout mice have been shown to retain sensitivity to the anorectic actions of PYY3-36 have suggested that the melanocortin system may not be essential for the mediation of the inhibitory effects of PYY3-36 on energy intake (Challis *et al.* 2004; Halatchev *et al.* 2004).

The effect of peripheral PYY3-36 on feeding has since been replicated in a number of species, including non-human primates (Challis *et al.* 2003; Adams *et al.* 2004; Halatchev *et al.* 2004; Pittner *et al.* 2004; Chelikani *et al.* 2005; Moran *et al.* 2005; Scott *et al.* 2005; Talsania *et al.* 2005), though with varying effects on gastric emptying. Furthermore, unlike CCK, this feeding effect does not appear to be subject to attenuation with more chronic administration of the peptide. Twice-daily IP injections of PYY3-36 for a period of seven days resulted in reduced food intake and weight gain in rats (Batterham *et al.* 2002).

In support of the hypothesis that peripherally administered PYY3-36 acts via the Y2 receptor, the peptide's anorectic actions are not seen in Y2-null mice (Batterham *et al.* 2002). Nor does endogenous or exogenous PYY3-36 inhibit feeding in rats that have been injected with BIIE0246, a selective antagonist of the Y2 receptor, directly into the ARC (Abbott *et al.* 2005*b*).

Evidence also exists, however, that runs counter to the 'leaky ARC' model described above, and some authors favour alternative mechanisms through which the anorectic effects of PYY3-36 may be mediated. Y2 receptor mRNA is also expressed in the NTS and the nodose ganglion of the vagus nerve (Gustafson *et al.* 1997; Koda *et al.* 2005). This observation and the reciprocal connections that exist between the ARC and NTS have led some investigators to suggest that PYY3-36 may inhibit feeding via an effect on the vagus. Abbott and co-workers have demonstrated that both bilateral subdiaphragmatic vagotomy and transectioning of the brainstem–hypothalamic neuronal pathways abolish the anorectic effects of peripheral PYY3-36. Interestingly, these procedures also attenuate the induction of *c-fos* in the ARC in response to PYY3-36, lending support to the case against an effect of circulating PYY3-36 directly on the ARC (Abbott *et al.* 2005*a*). Similar observations have been made by other researchers (Koda *et al.* 2005). Clearly, a comprehensive model of the mechanism of appetite regulation by PYY3-36 will need to bring together these disparate and occasionally contradictory observations.

Controversy also extends to the robustness of the suppression of caloric intake seen with both acute and chronic peripheral administration of PYY3-36. Some groups have had difficulty in replicating the initial findings of Batterham *et al.* (Tschop *et al.* 2004). The reasons for this are unclear, but seem to be confined to rodents. Stress is known to reduce food intake in rodents through effects in the ARC (Halatchev *et al.* 2004), and differences in acclimatization to the experimental procedure may account for the lack of efficacy of PYY3-36 in some studies. The effect in primates appears to be more robust, and arguably provides a better model for appetite regulation in humans.

(iv) *Role in humans*

That PYY3-36 performs a significant role in the control of appetite in humans is supported by a number of observations. In disease states characterized by weight-loss, such as inflammatory bowel disease, tropical sprue and cardiac cachexia, PYY3-36 levels are elevated (Adrian *et al.* 1986; El Salhy *et al.* 2002; Le Roux *et al.* 2005). Gastrointestinal surgery currently constitutes the most effective treatment for obesity, and the mechanism by which surgery effects weight loss is thought to involve a loss of appetite (Atkinson & Brent 1982). This appetite loss may be secondary to changes in the signals of energy balance released by the gut (Hanusch-Enserer & Roden 2005). In particular, gastric bypass surgery has been shown to result in an exaggerated postprandial PYY3-36 response, which may contribute to the durability of postoperative weight loss (Alvarez *et al.* 2002; Korner *et al.* 2005). Conversely, in obese humans, fasting plasma concentrations of PYY3-36 are reduced (Batterham *et al.* 2003*a*) and overweight subjects have a relative deficiency of postprandial PYY3-36 release associated with reduced satiety.

Intravenous infusion of PYY3-36 at a rate of 0.8 pmol $kg^{-1}$ $min^{-1}$ into lean humans increased mean plasma PYY3-36 levels from 8.3 to 43.5 pM, and mimicked postprandial PYY3-36 concentrations (Batterham *et al.* 2002). Plasma PYY3-36 returned to baseline concentrations within 30 minutes of the end of the infusion. Despite this, at a free-choice buffet meal 2 hours after the end of the infusion, there was a significant reduction in calorie intake of approximately 36%, with no effect on fluid intake or on gastric emptying as assessed by paracetamol absorption (Batterham *et al.* 2002).

Despite lower basal levels of PYY3-36 in obese humans, obesity does not appear to be associated with resistance to the effects of PYY3-36. Infusion of PYY3-36 into a group of obese volunteers resulted in a comparable reduction in calorie intake when compared with lean controls (Batterham *et al.* 2003*a*). This preservation of the effects of PYY3-36 in the obese, in the context of apparent abnormal postprandial release of the hormone, raises the possibility that PYY3-36 may be involved in the pathogenesis of obesity, and is therefore an attractive therapeutic target. Both Merck & Co. and Amylin Pharmaceuticals are currently in various stages of development of PYY3-36-based therapies for obesity.

### (c) *Pancreatic polypeptide*

PP is principally released by a population of cells located at the periphery of the pancreatic islets, although some is also synthesized in the exocrine pancreas and distal gut (Larsson *et al.* 1975; Adrian *et al.* 1976; Ekblad & Sundler 2002). In contrast to

other gut hormones, the presence of PP in the CNS is a matter of debate. Early reports of widespread PP-like immunoreactivity have now largely been ascribed to cross-reaction of the antibodies used with NPY (DiMaggio *et al.* 1985). Some researchers have reported the presence of PP immunoreactivity in extracts of porcine hypothalamus, pineal gland, substantia nigra, hippocampus and pituitary gland (Inui *et al.* 1985), but other groups have failed to demonstrate the presence of PP mRNA in the brains of rodents (Ekblad & Sundler 2002), and the matter remains unresolved.

PP secretion into the circulation is subject to an underlying circadian rhythm, with levels in fasting individuals increasing gradually during the day to peak at approximately 21.00 hours, before falling and reaching a nadir at 02.00 hours (Track *et al.* 1980). However, food intake is the main stimulus to PP secretion, and feeding promotes release of the hormone into the blood. The biphasic manner of this release becomes more marked over the course of the day and the percentage contribution of the first phase of PP release increases with each subsequent meal (Track *et al.* 1980). Postprandial PP release is proportional to the caloric intake and plasma levels remain elevated for up to 6 hours after feeding (Adrian *et al.* 1976).

Both basal and postprandial PP release is subject to control by the vagus nerve. Evidence of vagal involvement takes the form of elimination of the circadian rhythm of PP secretion and a marked reduction in postprandial release by propantheline, a drug with antimuscarinic actions (Track *et al.* 1980). Truncal vagotomy and atropine, another antimuscarinic agent, have also been shown to reduce meal-induced PP release in dogs (Niebel *et al.* 1987), and humans (Konturek *et al.* 1987; Meguro *et al.* 1995). PP secretion is also controlled by other factors, including the gut hormones ghrelin, motilin and secretin, all of which stimulate PP release, and somatostatin, which potently inhibits (Funakoshi *et al.* 1989; Gomez *et al.* 1997; Mochiki *et al.* 1997; Arosio *et al.* 2003).

More recent studies in which human PP was infused into healthy subjects have suggested that PP may exert an inhibitory effect on gastric emptying, as well as delaying the postprandial rise in insulin (Schmidt *et al.* 2005). A delay in gastric emptying is also seen in mice injected IP with murine PP (Asakawa *et al.* 2003). The early infusion studies in humans used bovine PP rather than native human peptide. Of the PP-fold proteins, PP shows the least conservation across species (Lundell *et al.* 1995). It is thought to be the most recently evolved of the family and to have arisen by duplication of the PYY gene (Hort *et al.* 1995). PP differs across species mainly in its N-terminus, which seems to be crucial for receptor recognition (Gingerich *et al.* 1991). While a species difference is one possible explanation for the discrepancy in the effects of PP on the stomach, bovine PP differs from the human protein by only two amino acids and demonstrates an affinity for the human Y4 receptor that is similar to human PP (Gehlert *et al.* 1996).

The function served by PP in signalling energy status is no less controversial. Genetically obese ob/ob mice lack PP cells in the pancreas, and replacement therapy with twice daily IP injections of bovine PP was found to reduce feeding and body weight gain (Malaisse-Lagae *et al.* 1977). Asakawa and co-workers have built upon this finding and have recently published work in which the effects of PP on energy balance in wild-type and genetically obese mice were extensively described. Synthetic murine PP injected IP into fasted mice significantly reduced feeding within 20 minutes of administration (the earliest timepoint studied) and this effect was apparent in cumulative feeding data over the 24 hours following injection (Asakawa *et al.* 2003). Repeated administration of PP over six days to ob/ob mice resulted in a significant reduction in body weight gain and an improvement in blood glucose and lipid profiles.

In humans, abnormal patterns of PP secretion have been found in patients with Prader–Willi syndrome, a disease entity characterized by hyperphagia and obesity (Zipf *et al.* 1981). The situation in non-syndromic obese patients is less clear. Some authors have reported an impairment of PP response (Lassmann *et al.* 1980; Glaser *et al.* 1988), whereas others report similar levels of circulating PP in obese subjects with stable body weight (Jorde & Burhol 1984; Meryn *et al.* 1986; Wisen *et al.* 1992). In anorexic individuals, there is evidence that PP responses are exaggerated (Uhe *et al.* 1992; Fujimoto *et al.* 1997). After gastric surgery, levels of PP in the circulation appear reduced (Amland *et al.* 1984; Meryn *et al.* 1986), though interestingly, levels seem to be increased after jejunoileal bypass, and may contribute to the weight loss associated with this latter operation (Jorde & Burhol 1982).

The effects of exogenous PP on appetite are less equivocal. When infused into subjects with Prader–Willi syndrome, PP induced a reduction in appetite and food intake (Berntson *et al.* 1993). Similarly, infusion intravenously into lean humans resulted in a decrease in appetite that persisted and was reflected in reduced food intake recorded in food diaries 24 hours after the infusion (Batterham *et al.* 2003*b*). It is this prolonged action of PP on food intake that makes it an attractive candidate for the development of an antiobesity therapy. This notion is supported by the observation that mice chronically over-expressing PP to supraphysiological levels are lean with reduced food intake (Asakawa *et al.* 2003), suggesting that chronic exposure to high levels of PP does not result in the development of resistance to the anorectic actions of the hormone.

As with PYY3-36, the mechanism through which PP effects its anorectic actions comprises a number of integrated elements. Some authors have suggested that the delay in gastric emptying seen with peripheral PP administration might underlie the inhibition of appetite (Katsuura *et al.* 2002), although others have demonstrated an appetite effect independent of changes in gastric motility (Batterham *et al.* 2003*b*). PP also increases oxygen consumption when administered IP to mice, supporting a role for increased energy expenditure in the mediation of weight loss by PP (Asakawa *et al.* 2003).

Vagal signalling appears to be necessary for the PP-mediated inhibition of feeding as this effect is abolished in vagotomized mice (Asakawa *et al.* 2003). In addition, changes in expression of a number of genes

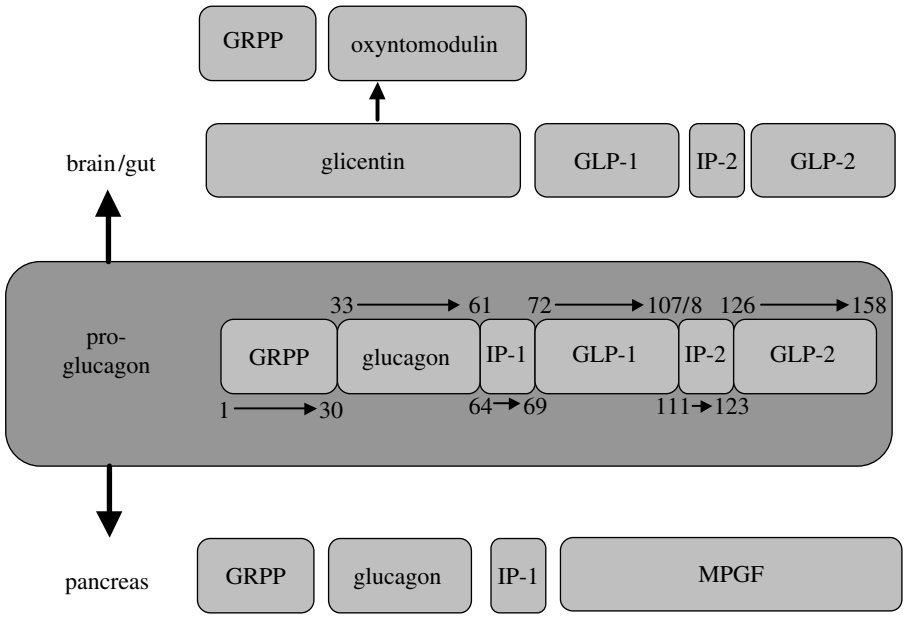


Figure 2. The products of preproglucagon cleavage. Numbers denote amino acid residues at which cleavage occurs. GLP-1 and GLP-2, glucagon-related peptides 1 and 2; GRPP, glicentin-related polypeptide; IP-1 and IP-2, intervening peptides 1 and 2; MPGF, major proglucagon fragment.

in the hypothalamus point to the involvement of CNS appetite circuits. IP injection of PP into fasted mice was shown to reduce mRNA expression in the hypothalamus of the orexigenic neuropeptides NPY and orexin by approximately 60%. Conversely, expression of mRNA of the anorectic urocortin was increased by 132%. A similar pattern of mRNA expression, though attenuated and not statistically significant when compared to control mice, was seen following IP injection of PP into non-fasted mice (Asakawa *et al.* 2003).

The interplay between these two sites of action is unclear. PP injected intracerebroventricularly (ICV) acts to increase food intake (Asakawa *et al.* 1999). As with PYY, this apparent non-concordance between the actions of CNS- and peripherally administered PP may be due to differential receptor activation and distribution. PP does not readily cross the blood–brain barrier (Banks *et al.* 1995), and thus may act preferentially in those areas of the hypothalamus that are more easily accessible due to a deficient blood–brain barrier. Alternatively, PP may act on the vagus nerve and thus modify the activity of hypothalamic circuits via projections from vagal nuclei in the brainstem. The area postrema in the brainstem also has an incomplete blood–brain barrier and demonstrates high binding of 125I-labelled PP *in vivo*, providing another level at which PP may directly act (Whitcomb *et al.* 1990).

Although it binds to all members of the Y receptor family, PP exhibits greatest affinity for the Y4 receptor subtype. Y4 receptor mRNA has been localized to areas of the hypothalamus, including the ARC (Parker & Herzog 1999). Receptor mRNA is also expressed widely in key appetite-regulating areas of the brainstem, including the area postrema (Larsen & Kristensen 1997).

In some species, including humans, though not in rats, PP also binds with moderately high affinity to Y5 receptors. In Y5 knockout mice, the orexigenic actions of CNS-injected human and bovine PP are blunted (Kanatani *et al.* 2000), suggesting involvement of the Y5 receptor in the stimulation of food intake by CNS PP. It has therefore been proposed that Y4 receptors accessible to circulating PP may be responsible for the mediation of the hormone's anorectic actions, whereas other receptors, such as Y5 receptors, might mediate the antagonistic effects of CNS-administered PP. Y4 receptors have, however, also been noted on orexin neurons in the lateral hypothalamic area (LHA). Injection of PP into the LHA stimulates feeding behaviour in rats, though to a lesser extent than injection of NPY. PP does, however, induce *c-fos* expression in LHA orexin neurons (Campbell *et al.* 2003). The integration of these observations into a unified model that explains the disparate actions of CNS and peripherally injected PP will require further data.

## 6. PRODUCTS OF PREPROGLUCAGON CLEAVAGE

Preproglucagon is a 160-amino acid prohormone with a 20-amino acid signal sequence at the N-terminal end (Kieffer & Habener 1999). It is synthesized in the $\alpha$-cells of the pancreatic islets, the L-cells of the intestinal mucosa and within the CNS. Preproglucagon undergoes differential cleavage by prohormone convertase 1 and 2, resulting in the tissue-specific production of a number of biologically active fragments (figure 2; Kieffer & Habener 1999). In the intestine and CNS, the products glucagon-like peptides-1 and -2 (GLP-1 and -2) and oxyntomodulin (OXM) have been implicated in the regulation of appetite, and will be considered in turn below. The actions of pancreatic glucagon on appetite are reviewed elsewhere in this issue. Briefly, peripheral administration induced satiety. Specifically, glucagon appears to affect the

processes related to meal termination and acts synergistically with other intermediaries, most notably CCK. Glicentin administered into rats ICV or directly into the PVN does not affect food intake (Dakin *et al.* 2001).

### (a) *Glucagon-like peptide-1*

GLP-1 is cleaved from preproglucagon within the intestine, where it is co-localized in the endocrine L-cells of the distal gut with OXM and PYY (Eissele *et al.* 1992; Wettergren *et al.* 1997). It is highly conserved across a number of species, implying an important physiological role.

Like PYY, GLP-1 exists in a number of forms in the circulation. GLP-1 is cleaved from preproglucagon as a 36- or 37-amino acid molecule, depending on whether the C-terminal glycine is present. Neither GLP-$1_{1\text{-}36amide}$ nor GLP-$1_{1\text{-}37}$ demonstrated significant biological activity. GLP-$1_{1\text{-}36amide}$ promotes insulin release from isolated rat pancreatic cells only at supraphysiological levels (Schmidt *et al.* 1985). It was with the realization that further N-terminal truncation is required for biological activity that the effects of GLP-1 were recognized (Mojsov *et al.* 1986). Both peptide isoforms are equipotent in those biological activities thus far examined, although GLP-$1_{7\text{-}36amide}$ is present in the circulation in greater quantities (Orskov *et al.* 1994*b*).

#### (i) *General physiology*

The action of GLP-$1_{7\text{-}36amide}$ that has attracted most attention, both from a physiological and a therapeutic viewpoint, is its potent incretin effect (Holst 2005). The peptide mediates glucose-dependent insulinotropic effects in a number of species, including man (Holst *et al.* 1987; Kreymann *et al.* 1987; Mojsov *et al.* 1987). It also inhibits gastric acid secretion and gastric emptying, as well as suppressing glucagon release and promoting an increase in pancreatic β-cell mass (Tolessa *et al.* 1998; Edvell & Lindstrom 1999; Naslund *et al.* 1999*b*). GLP-$1_{7\text{-}36amide}$ also exerts effects in the cardiovascular system. In animals, these appear to be stimulatory and to involve CNS and adrenal mechanisms (Edwards *et al.* 1997; Yamamoto *et al.* 2002). In humans, the situation is less clear, and in fact GLP-$1_{7\text{-}36amide}$ infusion may improve outcomes post-myocardial infarction in some circumstances (Nikolaidis *et al.* 2004).

Consistent with its role as an incretin, GLP-$1_{7\text{-}36amide}$ is released into the circulation in response to a meal in proportion to the calories ingested (Ghatei *et al.* 1983; Kreymann *et al.* 1987; Orskov *et al.* 1994*a*). Although the majority of L-cells are located in the distal gut, the presence of nutrients in the proximal small intestine stimulates GLP-$1_{7\text{-}36amide}$ release independently of the presence of nutrients within the ileum and colon (Roberge & Brubaker 1991). This effect is abolished by vagotomy, implying the influence of neural inputs on GLP-$1_{7\text{-}36amide}$ release (Rocca & Brubaker 1999). The similarity of this mechanism to that governing the release of PYY3-36 has led to the proposal of GLP-$1_{7\text{-}36amide}$ as another candidate mediator of the 'ileal brake' phenomenon.

#### (ii) *Role in energy balance*

Lately, however, increasing research has been directed at dissecting out the role of GLP-$1_{7\text{-}36amide}$ in the regulation of energy balance. In common with other gut peptides, GLP-$1_{7\text{-}36amide}$ also functions within the CNS as a neurotransmitter. It is present within the dorsovagal complex, the thalamus and the pituitary. GLP-1-immunoreactive neurons are also found in key areas of the hypothalamus involved in appetite-regulation, including the PVN and the DMH (Kreymann *et al.* 1989; Larsen *et al.* 1997*a*).

Further evidence for the involvement of GLP-$1_{7\text{-}36amide}$ in signalling energy status to CNS appetite circuits includes the distribution of the GLP-$1_{7\text{-}36amide}$ receptor. The GLP-1 receptor was originally cloned by selective screening of a rat pancreatic cDNA library, and the human homologue was subsequently isolated (Thorens 1992; Dillon *et al.* 1993). It is a G-protein-coupled, seven-transmembrane domain protein and binding of GLP-$1_{7\text{-}36amide}$ results in an increase in intracellular cyclic AMP (Gallwitz *et al.* 1993). Binding studies and reverse transcriptase polymerase chain reaction (RT-PCR) data for receptor mRNA have confirmed the presence of GLP-1 receptors in a number of areas of the brain important in appetite control. These include the ARC, the PVN and the supraoptic nucleus (SON) of the hypothalamus and the area postrema of the brainstem (Wei & Mojsov 1995; Shughrue *et al.* 1996).

Finally, the peptide exendin-4 has proved a useful tool in determining the mechanisms by which the actions of GLP-$1_{7\text{-}36amide}$ on appetite are mediated. This is a 39-amino acid peptide extracted from the saliva of the Gila monster, *Heloderma suspectum*. It is structurally related to GLP-1 and is a potent agonist at GLP-1 receptors, whereas the truncated form, exendin$_{9\text{-}39}$, acts as a competitive antagonist (Thorens *et al.* 1993). Recently, evidence has been accumulating that some of the actions of GLP-$1_{7\text{-}36amide}$ in some organs, notably adipose, muscle and liver tissue, may be mediated by an alternative GLP-1 receptor. The activity of GLP-1 at its receptor in these tissues is associated with a decrease in intracellular cAMP, in contrast to its actions at its recognized receptor. This putative alternative receptor also appears to be stimulated by both full-length exendin-4 and exendin$_{9\text{-}39}$, again contrasting with the antagonistic effects of exendin$_{9\text{-}39}$ at the established GLP-1 receptor (Montrose-Rafizadeh *et al.* 1997; Yang *et al.* 1998). The role played by this novel receptor in the appetite-regulating actions of GLP-$1_{7\text{-}36amide}$ remains to be clarified.

Both CNS-injected and peripherally administered GLP-$1_{7\text{-}36amide}$ inhibit food intake in a number of species. In both instances, the site of action appears to be the brainstem–hypothalamus axis.

Turton *et al.* administered GLP-$1_{7\text{-}36amide}$ via the ICV route to rats and demonstrated a significant inhibition of food intake. This effect was associated with induction of *c-fos* in the PVN and the central nucleus of the amygdala. Both the feeding effect and the induction of *c-fos* were inhibited by the presence of exendin$_{9\text{-}39}$. Significantly, exendin$_{9\text{-}39}$ alone had no effect in fasted rats, but powerfully increased feeding in satiated rats, implying the involvement of central

GLP-$1_{7\text{-}36amide}$ signalling in the physiological regulation of appetite (Turton *et al.* 1996). Furthermore, repeated ICV injection of GLP-$1_{7\text{-}36amide}$ into rats over six days resulted in a significantly reduced body weight when compared with saline-injected animals (Meeran *et al.* 1999). Again, injection of exendin$_{9\text{-}39}$ resulted in the opposite effect, suggesting underlying physiological GLP-$1_{7\text{-}36amide}$ signalling in the regulation of feeding behaviour in rats.

Other groups have subsequently confirmed this finding, and reported activation of *c-fos* by GLP-$1_{7\text{-}36amide}$ in other areas of the brain. These include the NTS and the area postrema in the brainstem, and the SON in the hypothalamus (van Dijk *et al.* 1996; Rowland *et al.* 1997; Larsen *et al.* 1997*b*). ICV-administered GLP-$1_{7\text{-}36amide}$ has also been reported to weakly induce *c-fos* within the ARC (van Dijk *et al.* 1996; Larsen *et al.* 1997*b*), although with such a high density of GLP-1 receptors localized in the ARC, it is perhaps surprising that the effect is not more pronounced.

(iii) *Appetite regulation versus visceral illness*

Mice lacking the GLP-1 receptor, while glucose intolerant, exhibit normal food intake and body weight (Scrocchi *et al.* 1996). Compensatory upregulation of alternative satiety pathways or alternative GLP-1 receptor types may underlie this observation, but coupled with the observation that ICV-injected GLP-$1_{7\text{-}36amide}$ may induce the phenomenon of conditioned taste aversion (CTA), this has led some investigators to question the physiological importance of GLP-$1_{7\text{-}36amide}$-induced anorexia.

In particular, the pattern of *c-fos* activation seen with ICV GLP-$1_{7\text{-}36amide}$ resembles that seen with administration of the toxin lithium chloride, a potent inducer of a visceral illness response in rodents (Kinzig *et al.* 2002; Lachey *et al.* 2005). Moreover, ICV administration of the GLP-1 receptor antagonist exendin$_{9\text{-}39}$ to rats is able to attenuate the effects of IP lithium chloride, suggesting that CNS GLP-1 is important in the visceral illness actions of lithium chloride (Seeley *et al.* 2000), although exendin$_{9\text{-}39}$ also binds to the receptors of other peptides, such as glucose-dependent insulinotropic polypeptide (Wheeler *et al.* 1995). Interestingly, the actions of lithium chloride are preserved in GLP-1 receptor null mice. In addition, ICV GLP-$1_{7\text{-}36amide}$ does not induce CTA in these knockout mice, whereas it does in their wild-type counterparts (Lachey *et al.* 2005). Species differences may account for the ability of lithium chloride to induce CTA in mice lacking the GLP-1 receptor, or it is possible that other minor pathways take on greater prominence in the absence of GLP-1 signalling.

When the data on energy intake and those on CTA are taken together, it is clear that GLP-$1_{7\text{-}36amide}$ injected ICV causes anorexia, but that the mechanisms underlying this, and the importance in a physiological setting, are the subject of contention. One model by which some of the divergent data may be reconciled is to invoke a role for GLP-$1_{7\text{-}36amide}$ in both the regulation of energy balance, and in the mediation of a visceral illness response, as distinct functions of the peptide. Injection of GLP-$1_{7\text{-}36amide}$ into the fourth and lateral ventricles gave rise to anorexia, but lateral ventricular administration also induced CTA. Direct injection into the central nucleus of the amygdala did not reduce food intake, but did induce CTA, suggesting that responses to GLP-1 in the PVN and brainstem are involved in the mediation of the peptide's anorectic effects, whereas CTA results from activation of amygdala GLP-1 receptors (Moran *et al.* 2005). An alternative model proposes that satiety and nausea are mediated by the same pathway, and that with low levels of stimulation, satiety predominates. Nausea results at high levels of stimulation of the pathway.

Peripheral administration of GLP-$1_{7\text{-}36amide}$ or GLP-1 receptor agonists such as exendin-4 into rodents also reduces feeding and induces *c-fos* expression in the brainstem and PVN, but not in the ARC (Tang-Christensen *et al.* 2001; Baggio *et al.* 2004; Dakin *et al.* 2004; Abbott *et al.* 2005*a*). The anorectic actions of IP GLP-$1_{7\text{-}36amide}$ are not attenuated by injection directly into the ARC of the receptor antagonist exendin$_{9\text{-}39}$ (Dakin *et al.* 2004). Furthermore, the observation that the effect of IP GLP-$1_{7\text{-}36amide}$ on feeding is reduced by vagotomy or ablation of brainstem–hypothalamic connections (Abbott *et al.* 2005*a*) raises interesting questions regarding the pathways through which GLP-$1_{7\text{-}36amide}$ acts to reduce food intake.

CNS-produced GLP-$1_{7\text{-}36amide}$ may act on appetite circuits within the brain, or GLP-$1_{7\text{-}36amide}$ released into the circulation postprandially may gain access to important areas of the hypothalamus and brainstem, and thus induce a feeling of satiety. These two scenarios are not mutually exclusive. An integrative model may best account for the importance of the vagus nerve and brainstem–hypothalamic connections, the effects of GLP-$1_{7\text{-}36amide}$ injected directly into specific hypothalamic nuclei such as the PVN and the pattern of *c-fos* induction seen on CNS and peripheral administration of the peptide. Circulating GLP-$1_{7\text{-}36amide}$ acting on the vagus, or entering the brainstem through the deficient blood–brain barrier at the area postrema (Orskov *et al.* 1996) may in turn influence neuronal activity in important hypothalamic nuclei. GLP-$1_{7\text{-}36amide}$ may itself be involved as a neurotransmitter in this process at the level of the hypothalamus or brainstem. Injection of a retrograde tracer confirmed that GLP-containing neurons project from the NTS to the PVN (Larsen *et al.* 1997*a*). Different circuits, involving the amygdala, may mediate GLP-$1_{7\text{-}36amide}$-induced nausea.

(iv) *Role in humans*

In humans, some authors have suggested that circulating GLP-$1_{7\text{-}36amide}$ levels are reduced in obesity, and normalize with weight loss (Verdich *et al.* 2001*b*). Other investigators, however, have failed to reproduce these findings (Feinle *et al.* 2002; Vilsboll *et al.* 2003).

The food intake data from human studies are concordant with the animal studies. GLP-$1_{7\text{-}36amide}$ dose-dependently decreases appetite and caloric intake in lean and obese humans and patients with diabetes (Gutzwiller *et al.* 1999*a*,*b*; Naslund *et al.* 1999*a*). Exendin-4 also reduced food intake when given to healthy volunteers (Edwards *et al.* 2001). In a recent

meta-analysis, it was concluded that infusion of GLP-$1_{7\text{-}36amide}$ reduces both appetite and food intake, the latter by an average of 11.7% acutely. The magnitude of this reduction is similar in lean and obese men. Furthermore, this was achieved without adverse effects on subject well-being, such as nausea (Verdich *et al.* 2001*a*).

(v) *Clinical potential*

This preservation of the anorectic effect of GLP-$1_{7\text{-}36amide}$ in the obese has led to interest in the therapeutic potential of the hormone. Prandial subcutaneous injections of GLP-$1_{7\text{-}36amide}$ given to obese but otherwise healthy subjects for 5 days resulted in a weight loss of 0.55 kg (Naslund *et al.* 2004).

One barrier to the use of native GLP-$1_{7\text{-}36amide}$ in a clinical setting is its short half-life. GLP-$1_{7\text{-}36amide}$ is a substrate for DPP-IV, although unlike PYY, the enzyme inactivates GLP-$1_{7\text{-}36amide}$. The half-life of a bolus of GLP-$1_{7\text{-}36amide}$ administered intravenously to rats is approximately 2 minutes, and this is extended to 10 minutes in DPP-IV-deficient rats (Kieffer *et al.* 1995). Although DDP-IV is not the sole route by which GLP-$1_{7\text{-}36amide}$ is degraded, any therapeutic application of GLP-$1_{7\text{-}36amide}$ would need to overcome this obstacle (Deacon 2004; Holst 2005). Two main strategies have been employed. Some pharmaceutical companies have developed potent long-acting GLP-1 receptor agonists, such as exendin-4 (exenatide, Amylin Pharmaceuticals), or albumin-based forms of GLP-1, such as liraglutide (NovoNordisk), that are resistant to the actions of DPP-IV. The other strategy comprises the use of DDP-IV inhibitors, such as that currently under development by Novartis. Of these, exenatide has recently been granted approval by the Federal Food and Drug Administration for use as an adjunctive therapy in poorly controlled type 2 diabetic patients, and all are at various stages of clinical testing for use specifically as therapies for obesity.

With the use of such gut hormone-based treatments, however, unforeseen side effects may arise. DPP-IV, for instance, plays a role in immune regulation (in which context it is known as CD26; Gorrell *et al.* 2001). Given its effects on β-cell proliferation, changes in plasma levels of GLP-1 following gastric bypass surgery have also been tentatively linked to the development of nesidioblastosis as a possible long-term postoperative complication (Service *et al.* 2005). Long-term safety data on GLP-$1_{7\text{-}36amide}$-based treatments is awaited.

One possible means by which the side effects of any therapy could be ameliorated might be to combine lower doses of two or more gut hormones in order to achieve the desired reduction in food intake. It is likely that physiologically, interactions between different gut hormones are just as important as the actions of the hormones themselves. Certainly, the co-localization of GLP-$1_{7\text{-}36amide}$ and PYY3-36 in the L-cells and their co-secretion in response to a meal argues in favour of a synergistic interaction. Indeed, co-administration of exendin-4 and PYY3-36 results in a larger reduction in food intake than either peptide alone at the same dose (Talsania *et al.* 2005). Theoretically, the side effect profile of such a therapeutic strategy in man would be superior to the use of higher doses of individual gut hormone-based treatments.

### (b) *Glucagon-like peptide-2*

Like GLP-$1_{7\text{-}36amide}$, GLP-2 is synthesized by the action of prohormone convertase 1 on preproglucagon in the CNS and intestinal L-cells (Damholt *et al.* 1999). It is released into the circulation in a biphasic manner following nutrient ingestion. Fat and carbohydrates are potent stimulators of GLP-2 release (Xiao *et al.* 1999). In common with other hormones secreted by L-cells in the distal gut, the early phase release appears to be mediated by a neuroendocrine reflex involving the vagus, whereas the later peak is likely a result of the action of intestinal nutrients directly on L-cells (Dube & Brubaker 2004).

GLP-2 acts via its own distinct seven-transmembrane domain receptor and increases intracellular cAMP levels (Munroe *et al.* 1999). This is distributed widely in the periphery and CNS. Through a combination of Northern blot, RT-PCR and immunocytochemical techniques, GLP-2 receptor mRNA has been detected in rat stomach, duodenum, jejunum, ileum and colon and in the hypothalamus, brainstem and lung (Yusta *et al.* 2000).

From the perspective of energy balance, GLP-2 injected ICV into rats does inhibit food intake (Tang-Christensen *et al.* 2000). Peripherally administered GLP-2, however, does not appear to affect energy intake in rodents, nor does it affect appetite and feeding in humans (Scott *et al.* 1998; Schmidt *et al.* 2003).

As with GLP-$1_{7\text{-}36amide}$, circulating GLP-2 is rapidly rendered inactive by the actions of DDP-IV (Xiao *et al.* 1999). This leaves open the possibility that DDP-IV inhibitors developed for their actions on GLP-$1_{7\text{-}36amide}$ may also prolong the plasma half-life of GLP-2, resulting in unwanted GLP-2-mediated side effects on the bowel such as uncontrolled cell growth.

### (c) *Oxyntomodulin*

The expression pattern of OXM (formerly known as enteroglucagon) mirrors that of the other preproglucagon-derived hormones discussed above. It is released into the blood following ingestion of food in proportion to the calories ingested (Ghatei *et al.* 1983; Le Quellec *et al.* 1992). Physiologically, it acts to reduce gastric motility and secretion in rodents and man (Dubrasquet *et al.* 1982; Schjoldager *et al.* 1988, 1989; Dakin *et al.* 2004). In addition, OXM has been found to exert an incretin effect (Schjoldager *et al.* 1988; Wynne *et al.* 2005*b*), though the magnitude of the rise in insulin is smaller than that seen with GLP-$1_{7\text{-}36amide}$ and some investigators have failed to detect any increase in postprandial insulin following administration of exogenous OXM (Cohen *et al.* 2003).

That OXM may be involved in appetite control is suggested not only by its distribution and secretion pattern, but also by observations of elevated plasma levels in illness characterized by weight loss, such as tropical sprue (Besterman *et al.* 1979). Additionally, OXM levels rise after gastric bypass surgery, paralleling the rise in levels of appetite-suppressing gut hormones such as GLP-$1_{7\text{-}36amide}$ and PYY3-36 (Holst *et al.* 1979; Sarson *et al.* 1981).

More direct evidence takes the form of experimental data. Injection of OXM ICV or into the PVN of fasted rats caused a reduction in food intake compared to controls (Dakin *et al.* 2001). The effect was also seen in non-fasted rats injected at the start of the dark phase, and OXM was of a comparable potency in reducing food intake to GLP-$1_{7\text{-}36\text{amide}}$ in its effects on feeding. IP injection of OXM was also found to reduce food intake in rats (Dakin *et al.* 2002). While some researchers have not found IP injection of OXM to lessen feeding in mice (Baggio *et al.* 2004), the findings have since been replicated in humans (Cohen *et al.* 2003). Intravenous infusion of OXM into lean volunteers resulted in a reduction of energy intake at a buffet meal of 19.3%, and 12 hour cumulative energy intake was also reduced by 11.3% (Cohen *et al.* 2003). Volunteers reported no nausea or adverse effects on meal palatability with infusion of OXM. Part of the mechanism by which OXM reduces appetite may involve suppression of the orexigenic hormone ghrelin (Cohen *et al.* 2003).

As well as short term effects on feeding, repeated administration of exogenous OXM results in a sustained reduction in caloric intake and weight loss in both rodents and humans. Repeated ICV injection of OXM into rats over 7 days resulted in a significantly lower body weight compared to both saline-injected controls and pair-fed saline injected controls. This suggests that the reduction in weight gain was brought about not only by a reduction in food intake, but also by an enhancement of energy expenditure (Dakin *et al.* 2002). Supporting this model, core temperature was noted to be higher in rats injected with OXM, and deposits of white and brown adipose tissue were found to be reduced. Similarly, repeated pre-prandial subcutaneous injection of OXM in obese human subjects resulted in a 2.3 kg reduction in body weight over the course of four weeks, compared with 0.5 kg in the saline-treated controls ($p=0.0106$; Wynne *et al.* 2005*b*).

A unique receptor for OXM has yet to be identified. OXM does bind to the GLP-1 receptor, but with an affinity that is approximately two orders of magnitude lower than GLP-$1_{7\text{-}36\text{amide}}$ (Fehmann *et al.* 1994). However, there is evidence, both circumstantial and more direct, that the effects of OXM may be mediated via the GLP-1 receptor. In *in vitro* assays, OXM is able to stimulate intracellular events in rat parietal cells enriched with the GLP-1 receptor (Schepp *et al.* 1996). The pattern of *c-fos* activation seen with peripheral administration of OXM in mice mirrors closely that seen with GLP-1 (Baggio *et al.* 2004). The anorectic effects of OXM are lost in GLP-1 receptor null mice, and are also inhibited by co-administration of the GLP-1 receptor antagonist exendin$_{9\text{-}39}$ (Dakin *et al.* 2001; Baggio *et al.* 2004).

Some data, however, are discordant with this model. Dakin *et al.* noted marked Fos-like immunoreactivity in the ARC in response to IP injection of OXM in rats (Dakin *et al.* 2004). While exendin$_{9\text{-}39}$ injected directly into the ARC inhibited the anorectic effects of IP OXM, it had no effect on the actions of GLP-$1_{7\text{-}36\text{amide}}$ on feeding (Dakin *et al.* 2004). Although the GLP-1 receptor is known to be present in the ARC (see above), exendin$_{9\text{-}39}$ exhibits a degree of non-specificity in its receptor binding, as discussed previously. It is therefore possible that OXM may act upon a novel receptor at which it is also antagonized by exendin$_{9\text{-}39}$.

Thus, although the physiological importance of its actions on appetite and energy intake remains uncertain, OXM offers another promising target in the development of a therapy for obesity. In particular, its less marked incretin effect compared to that mediated by GLP-$1_{7\text{-}36\text{amide}}$ may make it a more attractive option in the treatment of non-diabetic obese patients.

## 7. GHRELIN AND MOTILIN

The gut hormones ghrelin and motilin are structurally related peptides released from distinct areas of the gastrointestinal tract. Both have been found to exert an orexigenic effect.

### (a) *Ghrelin*

Ghrelin is the endogenous ligand for the previously orphan growth hormone secretagogue (GHS) receptor (Kojima *et al.* 1999). Briefly, the major source of circulating ghrelin is the stomach, although mRNA is also present elsewhere in the gastrointestinal tract (Kojima *et al.* 1999; Date *et al.* 2000). Among its actions, ghrelin stimulates growth hormone secretion from the anterior pituitary, stimulates the hypothalamo–pituitary–adrenal axis, mediates an increase in gastric motility, induces a positive inotropic effect on the heart and causes vasodilatation (Korbonits *et al.* 2004; van der Lely *et al.* 2004).

It is a peripherally active appetite-stimulating gut hormone. Levels rise during fasting, and fall upon eating, which has led to the suggestion that ghrelin may be involved in meal initiation (Cummings *et al.* 2001). Plasma levels of ghrelin are inversely correlated with body weight in humans and rise after weight loss (Cummings *et al.* 2002). An increase in ghrelin levels may explain why some individuals find weight loss difficult to maintain and have a tendency to regain weight after a period of dieting. The lower levels of ghrelin seen in obesity may constitute a feedback mechanism to reduce appetite (Tschop *et al.* 2001). Systemic injection of ghrelin increases food intake in rodents and man and chronic administration induces obesity in rodents (Tschop *et al.* 2000; Wren *et al.* 2001*a*,*b*).

From a clinical perspective, preliminary work has been carried out to investigate the effects of administration of ghrelin in diseases characterized by cachexia. Infusion of ghrelin into subjects with appetite loss due to cancer (Neary *et al.* 2004) increased energy intake by 31% at a subsequent buffet meal. This compares with an increase in energy intake of 28% when ghrelin was administered to healthy human volunteers (Wren *et al.* 2001*a*). The patients with cancer had high baseline plasma ghrelin levels, possibly as a reflection of negative energy balance. The ability of exogenous ghrelin to overcome the anorexia associated with cancer, to a similar degree as that seen in healthy subjects, and despite elevated endogenous ghrelin may make

manipulation of GHS receptors a rewarding strategy in the treatment of conditions associated with cachexia.

The intravenous route, it may be argued, is impractical, but a recent study has built upon the findings of the earlier work, and specifically considered the effectiveness of subcutaneously injected ghrelin in patients with chronic renal failure and mild to moderate malnutrition (Wynne *et al.* 2005*a*). Results were again encouraging, with energy intake more than doubled acutely following injection and maintained for 24 hours after the intervention. In particular in these patients with renal dysfunction, no acute adverse cardiovascular effects were noted. Indeed, other investigators have found that ghrelin may improve cardiac function and exercise capacity in patients suffering from chronic heart failure (Nagaya *et al.* 2004).

### (b) *Motilin*

Released by cells in the upper part of the duodenum (Usellini *et al.* 1984), circulating motilin levels peak every 100 minutes in the fasted state and fall postprandially (Itoh 1997). Its main physiological role is thought to be as a regulator of interdigestive gut motility. It also stimulates gallbladder contraction and enzyme secretion in the stomach and pancreas (Itoh 1997).

A number of authors have reported the presence of motilin in the CNS, as evidenced by the presence of motilin immunoreactivity in a number of brain areas in a variety of species (O'Donohue *et al.* 1981; Beinfeld & Bailey 1985). Other investigators, however, question the accuracy of the detection methods (Nilaver *et al.* 1988).

ICV injection of motilin into rodents has an orexigenic effect (Rosenfeld & Garthwaite 1987; Asakawa *et al.* 1998). IP injection of motilin at doses of 5 and 10 $\mu g\,kg^{-1}$ stimulated feeding in rats. Interestingly, this effect was seen only in fasted, but not fed, rats (Garthwaite 1985). Injection of 100 $\mu g\,kg^{-1}$ IP, however, has been found to inhibit feeding, without a detectable affect on behaviour otherwise (Olson *et al.* 1980). It is possible that this effect on feeding may be secondary to the hormone's primary actions on gut motility. The function of motilin in the physiological regulation of food intake therefore awaits better definition.

## 8. SOMATOSTATIN

Synthesis of this well-characterized hormone occurs in many organ systems throughout the body, where it fulfils myriad autocrine, paracrine, endocrine and neurocrine functions. A detailed description of the physiology of somatotrophin release inhibitory factor (SRIF; somatostatin) is beyond the scope of this review. However, within the alimentary tract, SRIF is synthesized in the D-cells of the gut and endocrine pancreas (Reichlin 1983). Its functions are broadly antisecretory. SRIF inhibits release of other hormones such as gastrin, CCK, secretin, motilin, vasoactive intestinal polypeptide and OXM, it inhibits gastric acid production, prolongs gastric emptying, reduces intestinal motility and decreases splanchnic blood flow, and it inhibits release of insulin, glucagon and release of exocrine pancreatic secretions (Reichlin 1983; Bell *et al.* 1995).

Similarly, the effects of SRIF on feeding are inhibitory, although it appears to reduce food intake only in animals with a mild degree of hunger (Lotter *et al.* 1981; Levine & Morley 1982). Feeding hydrolysed gluten to humans physiologically increases somatostatin levels in the circulation, but this had no effect on feeding or appetite (Morley *et al.* 1983). Thus the physiological importance of this effect of SRIF is unclear.

The mechanisms by which SRIF might act to reduce appetite are largely unresearched. Vagotomy abolishes the effect (Levine & Morley 1982). It may be that this mild effect on food intake is brought about indirectly, by reducing levels of ghrelin (Silva *et al.* 2005), although desensitization to the inhibitory effects of SRIF on circulating ghrelin may preclude any therapeutic application of this effect.

## 9. OTHER GASTROENTEROPANCREATIC PEPTIDES

A number of other peptides also affect food intake. One of these, amylin, is now available as an adjunctive therapy for diabetic patients with poor glycaemic control and is currently undergoing trials as a treatment for obesity *per se* (pramlintide, Amylin Pharmaceuticals). It is co-secreted with insulin by pancreatic β-cells and inhibits gastric secretion and emptying (Ludvik *et al.* 1997). Both ICV and peripheral injection of amylin inhibits food intake (Chance *et al.* 1991, 1993; Lutz *et al.* 1994; Rushing *et al.* 2000). This appears to be independent of the vagus nerve (Lutz *et al.* 1995).

Apolipoprotein A-IV (apoA-IV) is a 46kDa protein synthesized by enterocytes in response to intake of lipids, and secreted together with triglyceride-rich lipoproteins (chylomicrons and very low density lipoproteins; Fujimoto *et al.* 1992). Physiologically, as well as functioning as a lipoprotein, it also inhibits gastric secretions and intestinal motility (Okumura *et al.* 1996; Glatzle *et al.* 2002). ApoA-IV is also present in the CNS, and in particular in the ARC (Liu *et al.* 2003). Fasting causes a marked reduction in hypothalamic expression of apoA-IV mRNA levels in the hypothalamus (Liu *et al.* 2001).

Peripheral administration of apoA-IV reduces feeding in rats without adversely affecting their behaviour (Fujimoto *et al.* 1992). Furthermore, ICV injection of apoA-IV also results in a decrease in food intake in rats, and ICV injection of apoA-IV antisera into rats promoted feeding during the light phase, when rats do not normally exhibit feeding behaviour, suggesting a role for tonic apoA-IV signalling in the hypothalamus in the regulation of feeding (Fujimoto *et al.* 1993). While these data are promising, much remains unknown about the mechanisms by which apoA-IV reduces food intake, about the physiological role of apoA-IV in the short- and long-term regulation of appetite, and about its interaction with more established intestinal satiety signals. Whether it will prove to

be the basis for a useful therapy for obesity remains to be seen.

Leptin, the hormone product of the *ob* gene, is mainly synthesized in white adipose tissue. Initial high expectations regarding its role in energy balance have been revised following recognition of the phenomenon of leptin resistance in the obese state. Leptin is also synthesized by cells in the gastric mucosa, however, raising the possibility that it may yet play a role in meal termination (Peters *et al.* 2005). Levels in the stomach, however, are comparatively low, and the physiological importance of gastric leptin remains uncertain.

## 10. CONCLUSIONS

In the century since the first gut hormones were described, much has been discovered regarding their physiological actions. As part of their function to optimize the digestive process, it was perhaps inevitable that they should also act to regulate appetite and food intake. The prize being sought is an effective treatment for one of the most pressing public health issues of the new millennium, and while there is much that we still do not understand, recent advances in our knowledge of the integration of endocrine and neurological signals as a means by which the periphery signals energy status to the brain could soon bring that prize within our grasp.

Owais Chaudhri is supported by the Wellcome Trust.

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