Oral Diseases (2009) 15, 18–26. doi:10.1111/j.1601-0825.2008.01492.x

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INVITED REVIEW
MEDICAL REVIEW

Gut hormones and appetite control

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The gastrointestinal tract is the largest endocrine organ in the body. It secretes more than 20 different peptide hormones, which serve both a local regulatory function and provide a means by which the gut can regulate appetite and satiety. As the worldwide prevalence of obesity reaches epidemic proportions, the importance of delineating the mechanisms which regulate food intake becomes even more urgent. There is now a substantial body of work in both rodent and human models demonstrating the effects of these peptides on appetite and work is underway to therapeutically manipulate the gut-brain axis for the treatment of obesity. In addition, it may also be possible to use our understanding of the entero-endocrine system to treat calorie-deficient states.
Oral Diseases (2009) **15**, 18–26

Keywords: gut hormones; appetite; hypothalamus; brain stem; vagus nerve; ghrelin; peptide YY; pancreatic polypeptide; glucagon-like peptide-1; oxyntomodulin; cholecystokinin; obesity

Introduction

Over the past three decades the pathways of appetite regulation by the gut-brain axis have become increasingly well delineated. Within the entero-endocrine system, several key effectors such as ghrelin, peptide YY (PYY), pancreatic polypeptide (PP), glucagon-like peptide-1 (GLP-1), oxyntomodulin (OXM) and cholecystokinin (CCK) have been identified as peptides released from the gastro-intestinal (GI) tract, which modulate the activity of 'appetite centres' within the central nervous system (CNS) such as regions of the hypothalamus and brain stem ultimately leading to a change in ingestive behaviour. As the worldwide prevalence of obesity and its associated morbidity and mortality increases (WHO, 1998), there has been an increasing momentum to translate these physiological findings into targeted pharmaceutical treatments. Furthermore, In addition, it may also be possible to use our understanding of the entero-endocrine system in the management of calorie-deficient states.

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Received 26 August 2008; accepted 27 August 2008

Ghrelin

Ghrelin is the only known orexigenic gut hormone. It is a 28 amino acid peptide hormone produced by the X/A-like endocrine cells in the oxyntic glands of the gastric fundus (Date *et al*, 2000). It is octanoylated at the serine residue at position 3 by the gastric, membrane-bound enzyme ghrelin O-acyltransferase (Yang *et al*, 2008), a posttranslational modification, which is essential for receptor-binding (Kojima *et al*, 1999) and passage across the blood brain barrier (BBB) (Kojima and Kangawa, 2005). Ghrelin binds to the growth hormone secretagogue (GHS) receptor, a G protein coupled receptor which is highly expressed in the hypothalamus, the pituitary gland and the brainstem (Guan *et al*, 1997; Bailey *et al*, 2000).

Ghrelin has been called the 'hunger hormone' because of its stimulatory effect on appetite and food intake following both intracerebroventricular (ICV) and intraperitoneal (IP) administration of ghrelin to freely feeding rats (Tschöp *et al*, 2000; Wren *et al*, 2000) and to both lean and obese humans (Wren *et al*, 2001; Druce *et al*, 2005). The chronic administration of ghrelin to rats leads to weight gain, which is not solely caused by the induced hyperphagia (Tschöp *et al*, 2000) and may be attributable to the increased expression of enzymes that promote fat storage in adipose tissue (Theander-Carrillo *et al*, 2006). Of note, despite the potent orexigenic effect of ghrelin, ghrelin knockout mice display a similar phenotype to that of the wild type (Sun *et al*, 2003).

Levels of circulating ghrelin rise in the fasted state, increasing nearly twofold immediately before a meal and falling to a nadir level 1 h after eating (Cummings *et al*, 2001). These findings have led to the proposal that ghrelin acts as a meal initiator. The observed postprandial fall in plasma ghrelin is proportional to ingested calories with fat causing less suppression than carbohydrate or protein (Monteleone *et al*, 2003; Callahan *et al*, 2004).

The effects of ghrelin on food intake are thought to be mediated within the CNS. The arcuate nucleus (ARC) of the hypothalamus is well established in the control of food intake (Dhillo, 2007) and is ideally located near the median eminence where the BBB is incomplete, thus rendering it susceptible to the effects of circulating factors. There are two key neuronal populations in the ARC. One co-expresses the orexigenic peptides neuropeptide Y (NPY) and agouti-related protein (AgRP) (Broberger *et al*, 1998). The other neuronal sub-population co-expresses the anorectic peptides α-melanocyte-stimulating hormone (α-MSH), derived from pro-opiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (Elias *et al*, 1998). NPY neurons express the GHS receptor (Willesen *et al*, 1999) and systemic administration of ghrelin induces a rise in the immediate early gene *c-fos* in these neurons, which is a well-established marker of neuronal activation (Sagar *et al*, 1988; Hewson and Dickson, 2000). Furthermore, antibodies to and antagonists of NPY and AgRP abolish ghrelin-induced feeding (Nakazato *et al*, 2001).

It has recently been demonstrated that the intracellular effect of ghrelin on NPY/AgRP neuron is mediated by alterations in intra-neuronal mitochondrial respiration through changes in uncoupling protein 2 (Andrews *et al*, 2008). These changes in intra-neuronal metabolism ensure that the bioenergetic demands of NPY/AgRP neurons firing in response to ghrelin are continuously met. NPY/AgRP neurons therefore represent a potential target for circulating ghrelin, however NPY-deficient ghrelin treated mice still respond to administered ghrelin with increased food intake and weight gain (Tschöp *et al*, 2000) and it is therefore possible that ghrelin also exerts its effects outside of the ARC.

One potential extra-hypothalamic site may be the brainstem via the action of the vagus nerve. Vagal afferents serve as the major connection between the gut and the nucleus of the solitary tract (NTS) of the brainstem which has outputs to the ARC. Vagotomy abolishes the food-deprivation ghrelin rise (Williams *et al*, 2003) and ghrelin does not stimulate food intake in patients who have had a surgical procedure involving the vagus nerve (le Roux *et al*, 2005b). Furthermore, blockade of the gastric vagal afferent in a rodent model abolishes ghrelin-induced feeding and prevents the ghrelin-induced rise in ARC *c-Fos* (Date *et al*, 2002).

Obese subjects have been found to have lower fasting ghrelin levels and reduced ghrelin suppression after a meal compared with normal weight controls (le Roux *et al*, 2005a). It has also been shown that ghrelin levels rise after diet-induced weight loss (Cummings *et al*, 2002), which may make maintenance of weight loss harder to achieve.

The well characterised orexigenic effect of ghrelin makes it an attractive therapeutic target. It has been shown to stimulate food intake in cancer patients (Neary *et al*, 2004) and in malnourished peritoneal dialysis patients (Wynne *et al*, 2005a). The neutralisation of circulating ghrelin has been shown to promote weight loss in diet-induced obese mice (Shearman *et al*, 2006) and it has been reported that following gastric bypass surgery, the level of circulating ghrelin is markedly reduced which may augment the weight-reducing effect of the surgery (Cummings *et al*, 2002). Further work is needed to determine whether manipulation of the orexigenic effect of ghrelin may lead to a novel therapy in the treatment of human obesity.

Peptide YY

Peptide YY is a member of the PP fold family of proteins to which NPY and PP also belong. PYY is so named because of the tyrosine residues at both the N and the C terminus, Y being the single letter abbreviation for tyrosine (Tatemoto and Mutt, 1980). It is a 36 amino acid peptide, produced and released from the L-cells of the gastrointestinal (GI) tract, in particular those of the colon and rectum (Adrian *et al*, 1985). Most circulating PYY is the N-terminally truncated form of the full length peptide, the 34 amino acid $PYY_{3\text{-}36}$ (Grandt *et al*, 1994).

Levels of circulating $PYY_{3\text{-}36}$ are low during fasting and peak in the second hour after a meal, remaining elevated for up to 6 h (Adrian *et al*, 1985). The peak level is influenced by the number of calories consumed and the composition of the food (Adrian *et al*, 1985).

The acute peripheral administration of $PYY_{3\text{-}36}$ leads to a reduction in food intake in rodents and in humans (Batterham *et al*, 2002). Initially, these rodent findings proved controversial as other groups had difficulty in reproducing the results (Tschöp *et al*, 2004). However, there is evidence that the failure to reproduce the anorectic effect of the peptide arose from stress in the animals and their lack of acclimatisation (Batterham *et al*, 2004; Halatchev *et al*, 2004).

All of the PP fold proteins exert their effects through the Y family of G protein coupled receptors of which 5 subtypes have been identified Y1, Y2, Y4, Y5 and Y6 (Blomqvist and Herzog, 1997). $PYY_{3\text{-}36}$ binds preferentially to the Y2 receptor (Y2R) (Keire *et al*, 2000), which is expressed on NPY neurons of the ARC (Broberger *et al*, 1997). The direct injection of $PYY_{3\text{-}36}$ into the ARC inhibits food intake as does the administration of a selective Y2 receptor agonist consisting of a peptide core corresponding to residues 25-36 of PYY (Lumb *et al*, 2007). The inhibitory effect of peripheral $PYY_{3\text{-}36}$ is attenuated in rats treated with Y2R antagonists (Batterham *et al*, 2002; Abbott *et al*, 2005a) and abolished in Y2R knockout mice (Batterham *et al*, 2002).

One model for the anorectic mechanism of action of $PYY_{3\text{-}36}$ is the direct inhibition of ARC NPY neurons with consequent disinhibition of ARC POMC neurons, which has been demonstrated in electrophysiological studies (Batterham *et al*, 2002). Furthermore, incubation of hypothalamic explants *in vitro* with $PYY_{3\text{-}36}$ leads to reduced NPY release and an increase in the secretion of α-MSH (Batterham *et al*, 2002).

However POMC may not be essential for the action of $PYY_{3\text{-}36}$ as the anorectic effect of the peptide is preserved in mice with deficient melanocortin signalling (Adams *et al*, 2004).

Interestingly, ICV administration of PYY_{3-36} stimulates food intake and, when chronically administered, leads to obesity in the experimental animals (Raposinho *et al*, 2001). It has been postulated that this may be attributable to the effect of PYY_{3-36} on Y1 and Y5 receptors of the second order neurons of the paraventricular nucleus (PVN), which receive inputs from the NPY and POMC neurons of the ARC and activation of which has been shown to stimulate food intake (Hu *et al*, 1996; Mullins *et al*, 2001).

The anorectic effect of peripherally administered PYY_{3-36} is seen in both lean and obese human subjects (Batterham *et al*, 2003a). This suggests that obesity is not a PYY-resistant state, which is important in terms of the therapeutic potential of PYY as an anti-obesity treatment. It must be added however that the effect of stress on the anorectic action of the peptide has called into doubt its therapeutic potential. Furthermore, pharmacological doses of peripherally administered PYY_{3-36} have been reported to lead to taste aversion in mice (Halatchev and Cone, 2005) and nausea in humans (Degen *et al*, 2005). However, at physiological doses of PYY_{3-36} these effects are less pronounced. Two pharmaceutical companies have now completed phase I trials of PYY analogues as a potential anti-obesity agent.

Pancreatic polypeptide

Like PYY and NPY, PP is a member of the PP fold peptide family. It is a 36 amino acid peptide, which shows low inter-species sequence conservation (Conlon, 2002). PP is synthesised and released by the PP cells of the pancreatic islets of Langerhans and to a lesser extent the colon and rectum. The circulating level of PP is low during fasting (Adrian *et al*, 1977) and rises postprandially in proportion to the ingested calorie load (Track *et al*, 1980).

The peripheral administration of PP to mice and humans reduces food intake (Malaisse-Lagae *et al*, 1977; Batterham *et al*, 2003b). In normal weight human volunteers, food intake was found to be reduced by a mean of 21.8% at a free-choice buffet meal and this effect persisted until the following morning (Batterham *et al*, 2003b).

As is the case with PYY_{3-36}, the effect on food intake of exogenously delivered PP depends on the route of administration. Whilst peripherally administered PP leads to a reduction in food intake, the central (ICV) administration of PP stimulates daytime food intake in satiated rats (Clark *et al*, 1984). This difference in effect between peripheral and central administration is likely to be because of different sites of receptor activation; Like PYY_{3-36}, PP signals through the Y family of receptors, preferentially binding to the Y4 and Y5 subtypes (Larhammar, 1996). PP cannot cross the BBB and therefore PP from the periphery can only exert a central effect at sites where the BBB is incomplete such as the area postrema (AP) of the brainstem, where the Y5 receptor is highly expressed (Whitcomb *et al*, 1990). Interestingly, PP stimulated food intake is blunted in Y5 receptor knockout mice (Kanatani *et al*, 2000) but is unchanged in an antisense model of reduced Y5 signalling (Flynn *et al*, 1999).

In addition to a satiety effect, it has been reported that PP reduces the rate of gastric emptying (Schmidt *et al*, 2005) although work from other groups does not support this finding (Adrian *et al*, 1981).

Genetically, obese ob/ob mice are leptin deficient and also lack pancreatic PP cells. The peripheral administration of PP to these animals reduces food intake and body weight (Malaisse-Lagae *et al*, 1977). Transgenic mice which overexpress PP also eat less and weigh less than wild type control animals (Ueno *et al*, 1999).

All of these findings suggest that PP could be important in the regulation of body weight and work is currently underway to develop PP as an anti-obesity agent (http://news.bbc.co.uk/1/hi/health/6262347.stm).

Glucagon-like peptide-1

Glucagon-like peptide-1 is a 30 amino acid peptide, released in response to food intake (Herrmann *et al*, 1995) by the L-cells of the small intestine and colon, the alpha cells of the Islets of Langerhans (Eissele *et al*, 1992) and neurons within the NTS of the brainstem (Jin *et al*, 1988). Its precursor pre-proglucagon is processed by prohormone convertase 1 and 2, which differentially produce glucagon, GLP-1, glucagon-like peptide-2 and OXM depending on the site of synthesis (Bell *et al*, 1983). GLP-1 is completely conserved between all mammalian species, which may indicate its physiological importance.

Levels of circulating GLP-1 rise after a meal and fasting reduces proglucagon expression in the small intestine (Hoyt *et al*, 1996). Both the ICV and intranuclear injection of GLP-1 into the PVN reduce food intake in rats (Turton *et al*, 1996). The ICV administration of the specific GLP-1 receptor antagonist exendin (9-39) to satiated rats increases food intake (Turton *et al*, 1996) and administration of the antagonist twice a day for 10 days significantly increases body weight in the treated animals (Bloom, 1997). Furthermore, when ICV exendin (9-39) is repeatedly co-administered with NPY it potentiates the increased food intake and bodyweight that is seen with NPY alone (Meeran *et al*, 1999).

It has been argued that some of the observed reduction in food intake might have been cause by GLP-1-induced malaise in the experimental animals. Central GLP-1 administration has been shown to elicit symptoms of visceral illness including conditioned taste aversion in rats (Thiele *et al*, 1997) with a pattern of *c-Fos* activation seen that is similar to that following administration of the toxin lithium chloride (LiCl) (Lachey *et al*, 2005). Furthermore, ICV administration of a GLP-1 antagonist attenuates the effects of IP administered LiCl (Seeley *et al*, 2000).

The peripheral administration of GLP-1 has an anorectic effect in humans (Gutzwiller *et al*, 1999; Verdich *et al*, 2001a) and reduces the rate of gastric emptying, which might also influence food intake (Näslund *et al*, 1998; Verdich *et al*, 2001a). Evidence exists that obese

subjects have reduced circulating GLP-1 and an attenuated postprandial release, which increases with weight loss (Verdich *et al*, 2001b). In addition, obese subjects are sensitive to the anorectic effect of peripherally administered exogenous GLP-1 (Näslund *et al*, 1999).

Glucagon-like peptide-1 binds with high affinity to regions within the brain which have been identified as critical in the mediation of food intake including the hypothalamic ARC, PVN and supraoptic nucleus (SON) (Kanse *et al*, 1988; Shughrue *et al*, 1996; Turton *et al*, 1996) and the NTS of the brainstem. The anorectic effect of IP GLP-1 is not attenuated by intra-arcuate administration of the GLP-1 receptor antagonist exendin (9-39) (Dakin *et al*, 2004) and the central administration of GLP-1 leads to *c-Fos* induction in the PVN and SON but only a mild rise in the ARC. GLP-1 leptin receptor-positive neurons have been identified in the NTS (Larsen *et al*, 1997), which receive afferent inputs from the vagus nerve and the anorectic action as well as the effect on gastric emptying of GLP-1 is abolished by vagal afferent denervation (Imeryüz *et al*, 1997; Abbott *et al*, 2005b).

Glucagon-like peptide-1 has an incretin effect such that it augments glucose-dependent insulin secretion (Drucker *et al*, 1988; Drucker, 2006). In addition, it inhibits glucagon release (Komatsu *et al*, 1989; Orskov *et al*, 1988). Mice with a null mutation of the GLP-1 receptor gene (GLP-1R−/−) show mild fasting hyperglycaemia and impaired glucose tolerance associated with defective insulin release after IP and oral glucose administration (Scrocchi *et al*, 1996). Interestingly, GLP-1R−/− mice exhibit normal eating behaviour and are of normal body weight.

Circulating GLP-1 has a half-life of 5 min because of renal clearance and inactivation by the plasma enzyme dipeptidyl peptidase-IV (DPP-IV). Exendin-4 is a GLP-1 receptor agonist extracted from the saliva of the Glia monster, Heloderma suspectum, which is DPP-IV resistant and has been developed as Exenatide and marketed as Byetta (Amylin Pharmaceuticals and Eli Lilly and Company). It is a long-acting agonist at the GLP-1 receptor, which has proved efficacious in the regulation of glucose homeostasis in type 2 diabetes mellitus (T2DM) (Buse *et al*, 2004; DeFronzo *et al*, 2005; Kendall *et al*, 2005). In addition, exogenous GLP-1 has been shown to reduce body weight in diabetic patients (Zander *et al*, 2002) however Exenatide is not licensed as a weight loss treatment and furthermore GLP-1 has been reported to cause hypoglycaemia in non-diabetic subjects (Todd *et al*, 2003). Specific DPP-IV inhibitors have also been developed, which are now being used clinically in the treatment of T2DM. These drugs increase the postprandial rise in GLP-1 and increase insulin secretion however, unlike GLP-1 agonists, DPP-IV inhibitors are weight-neutral (Ahrén *et al*, 2004).

Oxyntomodulin

Oxyntomodulin derives its name from early work on the peptide, which identified its inhibitory action on the oxyntic glands of the stomach (Dubrasquet *et al*, 1982). Like GLP-1, OXM is a cleavage product of preproglucagon processing within entero-endocrine L-cells of the intestine and CNS. It is co-secreted with GLP-1 and PYY_{3-36} following ingestion of a meal and its release is proportional to the ingested calories (Ghatei *et al*, 1983; Le Quellec *et al*, 1992).

Oxyntomodulin is now well established as a gut peptide, which promotes satiety in both rodents and humans. The central administration of OXM to rats reduces food intake and this is seen following both ICV and intranuclear injection directly into the PVN (Dakin *et al*, 2001) and the ARC (Dakin *et al*, 2004).

A specific OXM receptor has not been identified and it has been postulated that OXM may signal through the GLP-1 receptor as the anorectic effect of IP OXM is blocked by the prior injection of the GLP-1 receptor antagonist exendin (9-39) into the ARC (Dakin *et al*, 2004) and abolished in GLP-1 receptor knockout mice (Baggio *et al*, 2004). Intriguingly, the injection of exendin (9-39) into the ARC does not block the anorectic actions of GLP-1, which might suggest that GLP-1 and OXM act via distinct pathways. Receptor-binding studies have shown that the affinity of OXM for the GLP-1 receptor is approximately two orders of magnitude lower than its affinity for GLP-1 (Dakin *et al*, 2001). The peripheral (IP) administration of OXM to rodents inhibits fast-induced and dark-phase food intake in a dose-dependent manner (Dakin *et al*, 2004). In this model, *fos*-like immunoreactivity was seen in the ARC, but little activity was observed in the neurons the brainstem, the latter being a pattern of neuronal activation seen following peripheral GLP-1 administration (Yamamoto *et al*, 2003).

Like GLP-1, OXM has been shown to have an incretin effect following glucose administration (Baldissera *et al*, 1988; Schjoldager *et al*, 1988) and, furthermore, OXM has been shown to exert a protective effect on pancreatic β cells in an experimental model of diabetes (Maida *et al*, 2008). Recently, it has been demonstrated that the glucoregulatory effect of OXM requires a functional GLP-1 receptor as the effect is abolished in GLP-1 receptor knockout mice (Maida *et al*, 2008).

The mechanism of the anorectic effect of OXM has not been fully characterised. Part of its suppressive effect on food intake may be caused by a reduction in plasma ghrelin. Infusion of OXM at postprandial concentrations leads to a fall in circulating ghrelin of 44% in human subjects and 15-20% in rodents (Cohen *et al*, 2003; Dakin *et al*, 2004). In addition, incubation of hypothalamic explants with OXM has been shown to cause a significant increase in the release of the anorectic ARC peptide α-MSH (Dakin *et al*, 2004).

Oxyntomodulin has also been shown to reduce food intake and body weight in human volunteers. In one study, the intravenous administration of OXM to human subjects reduced food intake by 19.3% at a buffet meal and cumulative 12 h food intake was also significantly reduced (Cohen *et al*, 2003). In another study, the preprandial subcutaneous administration of OXM to overweight and obese humans over 4 weeks led to a significant reduction in body weight of 2.3 kg compared with 0.5 kg in the control group (Wynne *et al*,

2005b). OXM administered over 4 days to human volunteers has been shown to increase total energy expenditure by almost 10% (Wynne *et al*, 2006). This finding may correlate with rodent data the analysis of which found that the repeated ICV administration of OXM to rats leads to a greater reduction in body weight compared to that of pair fed controls (Dakin *et al*, 2002). This additional effect of OXM administration is exciting as restrictive dieting usually leads to a fall in energy expenditure thereby impeding weight loss. Clinical trials are now underway looking at the potential of OXM as an anti-obesity therapy. In the human study of Wynne *et al*, 2005b, OXM was given by subcutaneous injection three times a day. This is because the anorectic effect of OXM is short lived which may in part be because of enzymatic inactivation in the plasma. Like GLP-1, OXM is inactivated by the enzyme DPP-IV and therefore development of an efficacious anti-obesity agent may depend on developing a peptide analogue, which is resistant to DPP-IV inactivation.

Cholecystokinin

Cholecystokinin was the first gut hormone reported to affect appetite (Gibbs *et al*, 1973). Levels of CCK in the plasma rise within 15 min of meal initiation (Liddle *et al*, 1985) and CCK has been shown to reduce food intake in a dose-dependent manner following its administration to rats (Gibbs *et al*, 1973) and to human subjects (Kissileff *et al*, 1981).

Cholecystokinin exists in several bioactive forms, CCK-8, CCK-22, CCK-33 and CCK-58, the numerical suffix denoting the number of amino acids. The predominant form in human plasma and intestine is CCK-33 (Rehfeld *et al*, 2001). CCK is widely distributed throughout the GI tract, but the majority is synthesised in the L-cells of the duodenum and jejunum (Buffa *et al*, 1976). In the GI tract, CCK exerts local regulatory effects including the stimulation of gallbladder contraction and pancreatic enzyme secretion (Liddle *et al*, 1985) and the inhibition of gastric emptying (Moran and McHugh, 1982). CCK is also widely distributed in the CNS including within the hypothalamus where it is most abundant in the ventromedial nucleus and the median eminence (Beinfeld *et al*, 1981).

Two CCK receptor subtypes, CCK_A and CCK_B have been characterised (Moran *et al*, 1986; Wank *et al*, 1992). CCK_A (which has also been called CCK_1) may be the more important receptor in the regulation of food intake because the administration of a selective CCK_A antagonist to rats reverses the inhibitory effect on food intake of IP CCK-8 (Melville *et al*, 1992). In addition, the Otsuka Long Evans Tokushima Fatty rat which has a null mutation of the CCK_A receptor is hyperphagic and obese (Moran *et al*, 1998); however, CCK_A knockout mice show no change in food intake compared with control animals (Kopin *et al*, 1999). The CCK_A receptor is expressed in the pancreas, vagal afferent and efferent neurons and is also found in the brain in the NTS, AP and dorsomedial hypothalamus, areas which are known to be important in the control of food intake (Moran

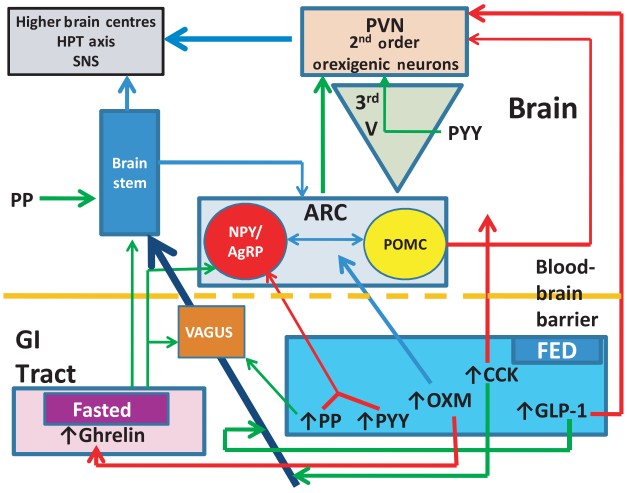

Figure 1 Schematic representation of gut hormone signalling to the central nervous system. In the fasted state, plasma ghrelin levels rise stimulating food intake (green arrows) via effects on the vagus nerve, brain stem and arcuate nucleus (ARC). Following a meal plasma levels of cholecystokinin (CCK), the panreatic polypeptide (PP) fold proteins PP and peptide YY (PYY) and the products of proglucagon cleavage, glucagon-like peptide-1 (GLP-1) and oxyntomodulin (OXM) rise inhibiting appetite via effects on the vagus nerve, brain stem and ARC. Red arrows indicate an anorectic effect. Blue arrows indicate that the effect may be stimulatory, inhibitory or is unknown. HPT, hypothalamo-pituitary-thyroid; SNS, sympathetic nervous system; PVN, paraventricular nucleus; 3rd V, third ventricle; NPY, neuropeptide Y; AgRP, agouti-related protein; POMC, pro-opiomelanocortin

et al, 1986). Abdominal or gastric vagotomy has been shown to block the satiety effect of peripherally administered CCK-8 indicating that CCK_A receptors on the vagus nerve may be particularly important in mediating the effect of CCK on food intake (Smith *et al*, 1981).

The peripheral administration of CCK to both rodents and humans leads to a reduction in food intake by reducing meal size and duration (Kissileff *et al*, 1981). At high doses, CCK has been reported to cause nausea, and taste- and place aversion (Deutsch and Hardy, 1977; Swerdlow *et al*, 1983; Mosher *et al*, 1998) but at low doses the anorectic effect of the peptide has been found to be not attributable to induced malaise in the experimental animal (West *et al*, 1987).

The central administration of CCK has also been shown to reduce food intake in rodents and this effect is augmented by the concomitant administration with leptin, leading to the possibility that CCK may play a role in the long-term regulation of body weight (Matson *et al*, 2000).

The therapeutic potential of CCK for use in the management of obesity has been considered. The intermittent peripheral administration of CCK over 6 days to free-feeding rats was found to reduce meal size by at least 44%, however, this was compensated for by an increase in meal frequency of 162% or more with no net change in body weight (West *et al*, 1984). In addition, it has been shown the constant IP infusion of CCK for 2 weeks rapidly leads to tolerance and hence no change in body weight or food intake (Crawley and Beinfeld, 1983). The short half-life of the peptide is a further barrier to its

therapeutic utility; the half-life of CCK is 1–2 min and if administered more than 15 min before a meal it fails to reduce meal size (Gibbs *et al*, 1973).

Conclusion

Research into the gut-brain axis is a fast growing field, which over the last 30 years has yielded a wealth of information about the crucial role that gut hormones play in the regulation of appetite and food intake (Figure 1). Throughout the world, the problem of obesity and its associated morbidity and mortality is reaching epidemic proportions (WHO, 1998). Whilst more work is needed to further delineate the physiological and pathophysiological roles of these peptides, it is becoming increasingly conceivable that these hormones could be therapeutically manipulated in the treatment of obese individuals.

Acknowledgements

SH is a Medical Research Council Clinical Research Training Fellow. WSD is funded by a Department of Health Clinician Scientist Award. The Department is funded by a Wellcome Trust, Medical Research Council Program Grant, the EU 6th Framework Programme DIABESITY (LSHM-CT-2003-503041), an Integrative Mammalian Biology (IMB) Capacity Building Award and funding from the NIHR Biomedical Research Centre Funding Scheme.

Author contributions

S Hameed, WS Dhillo and SR Bloom drafted the manuscript.

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