Invited review

The role of the gut/brain axis in modulating food intake

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ABSTRACT

Peptide hormones released from the gastrointestinal tract communicate information about the current state of energy balance to the brain. These hormones regulate appetite and energy expenditure via the vagus nerve or by acting on key brain regions implicated in energy homeostasis such as the hypothalamus and brainstem. This review gives an overview of the main gut hormones implicated in the regulation of food intake. Research in this area has provided novel targets for the pharmacological treatment of obesity.

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1. Introduction

Hormones released from the gut and adipose tissue play an important role in the regulation of food intake and energy expenditure. These hormones may exert their effects both via the vagus nerve and by acting directly on areas of the brain implicated in the control of energy homeostasis. Peripheral signals from the gut and adipose tissue constitute feedback mechanisms allowing maintenance of a steady body weight, despite daily variations in energy expenditure and nutrient intake.

The role of peripheral hormones and the gut/brain axis in the regulation of appetite has become an area of interest in recent years, owing to the growing global obesity crisis. Obesity is a major worldwide public health problem, with a significant burden of morbidity and mortality, as well as having substantial economic consequences. It is an important risk factor for type 2 diabetes, ischaemic heart disease, stroke and cancer, and carries an increased risk of both all cause, and cause-specific mortality (Prospective Studies Collaboration, 2009; Ringback Weitoft et al., 2008; Zheng et al., 2011). Peripheral signals controlling satiety may present potential targets for developing novel anti-obesity therapies. The focus of this review is to provide a synopsis of the gut-brain cross talk involved in the regulation of food intake.

2. Neuroendocrine control of appetite (Fig. 1)

The hypothalamus and the brainstem are the main central nervous system regions responsible for the regulation of energy homeostasis. These brain areas receive peripheral neural and hormonal signals that relay information about acute nutritional state and adiposity (Murphy and Bloom, 2006). Neural afferents and hormonal signals from the periphery are integrated with higher brain centre signals (e.g. relaying reward drive and mood) to regulate appetite and control energy expenditure (Schwartz et al., 2000).

The arcuate nucleus (ARC) of the hypothalamus is believed to play a crucial role in the regulation of food intake and energy homeostasis. This nucleus contains two populations of neurons with opposing effects on food intake (Chaudhri et al., 2008). Medially located orexigenic neurons (i.e. those stimulating appetite) express neuropeptide Y (NPY) and Agouti-related protein (AgRP) (Bewick et al., 2005; Broberger et al., 1998; Hahn et al., 1998). Anorexigenic neurons (i.e. those inhibiting appetite) in the lateral ARC express alpha-melanocytostimulating hormone (alpha-MSH) derived from pro-opiomelanocortin (POMC), and cocaine- and amphetamine-regulated transcript (CART) (Elia et al., 1998).
The ARC is adjacent to the median eminence, a ‘circumventricular organ’ with fenestrated capillaries and hence an incomplete blood—brain barrier (Peruzzo et al., 2000). Circulating hormones can therefore influence the activity of the arcuate nucleus neurons directly, after passing across the median eminence. Gut hormones, released from the gastrointestinal tract on a meal to meal basis, signal short-term nutrient availability to the ARC. Other circulating factors such as insulin and leptin (a circulating peptide released from adipose tissue) relay information regarding long-term circulating factors such as insulin and leptin (a circulating peptide).

Enteroendocrine cells of the gastrointestinal tract

There are at least 15 different types of enteroendocrine cells diffusely distributed throughout the gastrointestinal epithelium (Sjolund et al., 1983). These cells produce and release a variety of hormones and signalling molecules, which together constitute the largest endocrine organ in the body (Cheng and Leblond, 1974; Sjolund et al., 1983). The enteroendocrine cells are derived from multipotent stem cells, located towards the base of the intestinal crypts. The different enteroendocrine cell subpopulations are constantly re-established by the differentiation of enteroendocrine cells arising from these stem cells. The majority of enteroendocrine cells undergo terminal differentiation as they migrate up from the crypts to the epithelial surface (Tsoubouchi and Leblond, 1979).

Immunohistochemical studies have shown that enteroendocrine cells frequently express two or more products. PYY has been shown to co-localise with glucagon-like peptide-1 (GLP-1), neuropeptide Y (NPY), and cholecystokinin (CCK) in enteroendocrine cells in the colon (Roth et al., 1992). Approximately 50% of CCK and NT cells co-express PYY (Roth et al., 1992). Substance P/serotonin cells are commonly found in the same crypts as PYY/GLP-1/CCK/NT cells and most of the substance P cells also contain serotonin. However, co-expression of substance P/serotonin in the same cells as PYY/GLP-1/CCK/NT is only rarely observed (Roth et al., 1992). This suggests the existence of two separate branches of enteroendocrine L-cell differentiation, with one branch resulting in cells producing substance P and serotonin, and the other resulting in GLP-1, PYY, NT, and CCK-producing cells (Roth et al., 1992).

Chemosensing of gut luminal contents by the enteroendocrine GI cells plays a critical role in the control of functions such as digestion, pancreatic secretion, food intake, and metabolic regulation. Evidence that entodermic cells can directly sense luminal contents has been demonstrated in PYY and GLP-1 expressing L cells. It has been shown that both human and rodent intestinal L cells express receptors previously identified in the oral epithelium for detecting sweet (T1R2 and T1R3) and bitter sensation (T2R), as well as amino acids (T1R1 and T1R3) (Jang et al., 2007; Rozengurt et al., 2006). The gustducin G protein associated with these taste receptors has also been identified in L cells of the gut (Jang et al., 2007; Rozengurt et al., 2006). The activation of these receptors leads to an increase in intracellular calcium levels and release of gastrointestinal peptides from enteroendocrine cells (Rozengurt et al., 2006). The presence of the sweet taste receptor subunit T1R3 and gustducin may also underlie a luminal glucose sensing mechanism, since activation of these receptors mediates the postprandial release of GLP-1 from intestinal L cells (Jang et al., 2007).

Fatty acids derived from digestion of dietary fats appear to be sensed via separate mechanisms. The short-chain fatty acid receptors GPR43 and GPR41 are expressed in PYY-containing enteroendocrine L cells (Karaki et al., 2006; Tazoe et al., 2009). Short-chain fatty acids have been shown to increase PYY secretion in rats when delivered directly into the colon (Cherbut et al., 1998;
Fu-Cheng et al., 1995). GPR119 is another G protein coupled receptor found in intestinal endocrine cells as well as pancreatic beta cells (Chu et al., 2008, 2007). Administration of oleoylthetanolamide (OEA), an endogenous long chain fatty acid derivative, and other GPR119 agonists increases GLP-1 secretion, both in vitro and in vivo in rodents (Chu et al., 2008; Lauffer et al., 2009).

The enteroendocrine L cells therefore have the capacity to integrate complex nutrient sensing in the gut and to respond appropriately by releasing gut hormones. In addition to chemical stimulation, the endocrine cells of the gut also respond to neural and physical stimulation of the cell by releasing peptide containing granules at the basolateral side of the cell. These peptides can have an endocrine role, a local paracrine role, and/or activate receptors present on nerves innervating the GI mucosa (Cummings and Overduin, 2007).

4. Gut hormones regulating food intake

The gastrointestinal tract releases more than 20 different regulatory peptide hormones that influence a number of physiological processes. Gut hormones act on tissues such as exocrine glands, smooth muscle and the peripheral nervous system (Murphy and Bloom, 2006). The release of gut hormones such as PYY, GLP-1, and oxyntomodulin (OXM) is stimulated by distension of the stomach and interactions between nutrients and the luminal wall of the intestine (Adrian et al., 1985; Le Quellec et al., 1992).

Gut hormones are believed to contribute to the short-term feelings of satiety and hunger (Radman and Flier, 2005). These peptides may reduce food intake by decreasing hypothalamic orexigenic signalling, and increasing anorectic signalling (Batterham et al., 2002; Jobst et al., 2004). Another effect of these peptides is to mediate inhibitory feedback mechanisms on intestinal transit, contributing to prolonged gastric distension, and increased satiety between meals (Lin et al., 1996; Wen et al., 1995). These combined CNS effects and ‘intestinal brake’ mechanisms, mediated by gut peptides such as CCK, PYY, GLP-1 and OXM, facilitate the control of food intake and post-prandial transit through the gastrointestinal tract.

5. Peptide tyrosine tyrosine (PYY)

PYY, like NPY and Pancreatic Polypeptide (PP), belongs to the ‘PP-fold’ family of proteins. These peptides are 36-amino acids in length and share a common tertiary structural motif known as the PP-fold. C-terminal amidation of these proteins is a necessary requirement for biological activity. PYY exists endogenously in two forms: PYY1-36 and PYY3-36 (Grandt et al., 1994). The enzymatic cleavage of secreted PYY1-36 at the amino terminal by the cell surface enzyme dipeptidyl peptidase IV (DPP-IV) gives rise to PYY3-36 (Medeiros and Turner, 1994), the predominant form of circulating PYY immunoreactivity.

Low levels of PYY are detected in enteroendocrine cells in the stomach, and levels increase distally along the small and large intestine, reaching their highest levels in cells in the colon and rectum (Adrian et al., 1985). Endogenous circulating concentrations of PYY are lowest in the fasting state, and rise post-prandially as PYY is released from enteroendocrine L cells lining the distal GI tract in proportion to caloric intake (Adrian et al., 1985). Plasma levels of PYY rise within 30 min of a meal, and in humans, circulating levels plateau at 1–2 h post-prandially, remaining elevated for up to 6 h (Batterham et al., 2003a). Protein rich meals cause the greatest increase in PYY levels compared to other macronutrients (Batterham et al., 2006; Pedersen-Bjergaard et al., 1996).

Peripheral administration of PYY3-36 reduces food intake and weight gain in rodents (Batterham et al., 2002; Challis et al., 2003; Chelikani et al., 2005; Vrang et al., 2006), and although there was initial controversy regarding the effects of PYY3-36 on food intake (Tschop et al., 2004), many groups have subsequently validated its anorectic effects (Chelikani et al., 2005; Vrang et al., 2006). Demonstration of the anorectic effect of PYY in rodents is dependent upon the full acclimatization of the animals to the handling and injection procedures, and is lost in the presence of even mild stressors (Abbott et al., 2006; Halatchev et al., 2004). This is because stress can reduce baseline food intake, making it difficult for anorectic agents to further suppress appetite. Intravenous administration of PYY inhibits food intake in humans and it is equally effective in normal and obese subjects (Batterham et al., 2003a).

The anorectic effects of PYY3-36 appear to be mediated centrally via the ARC, as peripheral administration of PYY3-36 has been shown to increase c-fos expression in this hypothalamic nucleus (Batterham et al., 2002). As discussed previously, the ARC contains two neuronal populations, orexigenic NPY/AgRP, and anorexigenic POMC/CART neurons. There is conflicting data regarding the effects of PYY3-36 on these neurons. Peripheral administration of PYY3-36 has been reported to decrease expression and release of NPY whilst activating POMC neurons (Batterham et al., 2002). However, other investigators have reported that PYY3-36 inhibits POMC neurons via postsynaptic Y2R (Ghamari-Langroudi et al., 2005). Moreover, POMC knockout mice maintain their acute anorectic response to peripherally administered PYY3-36, suggesting that POMC is not critical to the inhibitory effects of PYY3-36 on feeding. PYY3-36 and PYY3-30 exert their effects through the neuropeptide Y family of receptors (Larhammar, 1996). PYY1-36 binds with similar affinity to all of the Y receptors, however PYY3-30 is a selective high affinity agonist at the Y2 receptor subtype (Y2R) (Grandt et al., 1992). The Y2R is thought to be the receptor responsible for mediating the reduction of food intake by PYY. It is an auto-inhibitory presynaptic receptor found on NPY neurons within the ARC (Broberger et al., 1997), and deficiency of the Y2R abolishes the anorectic effects of PYY (Batterham et al., 2002). Furthermore, the anorectic effects of PYY3-36 are attenuated by Y2R antagonists (Abbott et al., 2005b). PYY3-36 is therefore thought to reduce food intake through activation of the Y2R.

A vagal brainstem mediated pathway may also be involved in the actions of circulating PYY3-36. PYY is present in myenteric nervous plexus neurons innervating the gastrointestinal tract and the Y2R receptor has been identified on the vagus nerve (Koda et al., 2005). The effects of peripheral administration of PYY3-36 on both food intake (Abbott et al., 2005a; Koda et al., 2005), and on the activation of ARC feeding neurons, are abolished following bilateral sub-diaphragmatic total truncal vagotomy or transection of the brainstem—hypothalamic pathway in rodents (Abbott et al., 2005a), supporting a role for the vagus in appetite regulation.

PYY has been shown to have an effect on intestinal motility. Close intra-arterial administration of PYY in cats causes an inhibition of jejunal and colonic motility (Lundberg et al., 1982). PYY also delays gastric emptying, decreases pancreatic secretions, and increases absorption of fluids and electrolytes from the ileum in humans (Savage et al., 1987; Symersky et al., 2005). It is possible that some of the anorectic effects of PYY may be mediated by the gastric distension resulting from delayed gastric emptying.

Interestingly, it has recently been shown that acute effects of gastrointestinal bypass surgery on body weight are lost in PyyKO mice (Chandarana et al., 2011), and that wild-type mice losing weight after gastrointestinal bypass surgery exhibit increased colonic PYY expression and circulating fasting PYY levels (Chandarana et al., 2011). This suggests that PYY plays a key role in mediating the early weight loss that occurs following gastrointestinal bypass surgery.

The effects of PYY3-36 on satiety and central control of appetite are clear. Most are mediated via anorectic neuronal populations in the ARC, but vagal/brainstem-mediated pathways and peripheral effects of PYY on gastric emptying and intestinal motility may also...
play a part. High plasma concentrations of PYY result in nausea, but the importance of PYY3–36 at physiological levels in the regulation of energy intake make it a prime focus for new obesity therapies, targeted either at PYY itself, or against the Y2 receptor.

6. Glucagon-like peptide-1 (GLP-1)

GLP-1 is a 30 amino acid peptide resulting from cleavage of the preproglucagon precursor molecule (Dhanvantari et al., 1996). The two bioactive forms of GLP-1, GLP-17–37 and GLP-17–36 amide, are released into the circulation from L cells of the gastrointestinal tract in response to an oral glucose load (Herrmann et al., 1995). Physiologically, GLP-1 is an important incretin, stimulating glucose-dependent insulin release (Macdonald et al., 2002). In addition to its incretin effect, GLP-1 also inhibits the secretion of glucagon, thereby inhibiting endogenous glucose production (Wills et al., 1996). The net effect is to reduce blood glucose following a meal. GLP-1 also delays gastric emptying (Schirra et al., 2006), and increases satiety (Punjabi et al., 2011).

Like PYY, GLP-1 has been shown to act centrally in hypothalamic nuclei known to be implicated in the control of appetite including the ARC, PVN and supraoptic nucleus (Shauhrue et al., 1996). Both acute and chronic administration of GLP-1 reduce food intake in rats (Tang-Christensen et al., 2001; Turton et al., 1996) and chronic administration of GLP-1 reduces weight gain (Meeran et al., 1999). The intravenous administration of GLP-1 to normal and obese humans decreases food intake in a dose dependent manner (Verdich et al., 2001) as well as reducing gastric emptying (Naslund et al., 1999; Nauck et al., 1997). These effects are thought to be mediated through vagal and brainstem pathways since peripheral administration of GLP-1 activates neurons within the brainstem in rats (Imeryuz et al., 1997). Furthermore, this increase in neuronal activity, and the anorectic effects of GLP-1, are abolished following vagotomy in rodents (Abbott et al., 2005a; Imeryuz et al., 1997), reinforcing the argument for vagal involvement. More recently, techniques such as functional magnetic resonance imaging (fMRI) have confirmed a change in signal intensity within neuronal populations in the VMH and the PVN following peripheral administration of GLP-1 (Parkinson et al., 2009). This adds further weight to the evidence that appetite and feeding are regulated by GLP-1 via these hypothalamic and brainstem areas.

GLP-1 is rapidly degraded in the circulation by the enzyme DPP-IV, making native GLP-1 unsuitable for therapeutic use. Longer acting GLP-1 mimetics have been developed as new treatments for type 2 diabetes (Joy et al., 2005). Exendin-4 is a naturally occurring GLP-1 mimetic isolated from the venom of Heloderma suspectum, a lizard native to several southwestern American states (Eng et al., 1992). A truncated form of this peptide, exendin 9–39, acts as a competitive antagonist at the GLP-1 receptor. Acute intracerebroventricular administration of exendin 9–39 increases food intake, and chronic administration increases body weight in rats (Meeran et al., 1999; Turton et al., 1996). Endogenous peripheral GLP-1 may physiologically reduce appetite and food intake after a meal. However, GLP-1 receptor knockout mice do not have altered food intake or body weight (Drucker, 2006). This may be because developmental changes compensate for the lack of GLP-1 signalling, or may reflect that GLP-1 has a more important physiological role in controlling blood glucose than in regulating food intake.

The discovery of exendin-4 has led to the development of a synthetic version, exenatide. Exenatide has a much longer in vivo half-life than GLP-1 and is the first incretin mimetic approved for the treatment of type 2 diabetes (Drucker and Nauck, 2006). Exenatide is effective at stimulating insulin release, suppressing glucagon and lowering blood glucose. Clinical trials have demonstrated that exenatide is useful for the treatment of type 2 diabetes mellitus. Exenatide has also been shown to reduce body weight in treated diabetics in phase III clinical trials (Buse et al., 2004; DeFronzo et al., 2005; Kendall et al., 2005). The weight loss associated with exenatide is considered a significant advantage as many anti-diabetic treatments are commonly associated with weight gain. Nausea is a relatively common side effect of the treatment. However, it does not seem to be intrinsically linked to the effects on appetite (Murphy and Bloom, 2006). Whilst GLP-1 has been developed as a treatment for diabetes due to its incretin properties, the observed effects of GLP-1 on satiety and weight loss are a valuable secondary effect. Indeed recent data suggests liraglutide maybe useful for the treatment of obesity, causing sustained weight loss over 2 years but with a 50% rate of nausea and vomiting in the 3.0 mg/day group in the first year (Astrup et al., 2011).

7. Oxymontomodulin (OXM)

OXM, like GLP-1, is also a product of the preproglucagon precursor molecule. It is a 37 amino acid peptide released post-prandially from L cells in proportion to caloric intake (Le Quellec et al., 1992). OXM delays gastric emptying and reduces gastric acid secretion (Schjoldager et al., 1989), and has been shown acutely to decrease food intake and in the longer term to decrease weight gain in rodents (Dakin et al., 2001, 2004). In addition, chronic administration of OXM causes rats to lose more weight than pair-fed controls, suggesting an increase in energy expenditure (Dakin et al., 2002). OXM also reduces food intake in normal weight human volunteers when administered intravenously or subcutaneously (Cohen et al., 2003). Given preprandially to obese subjects it reduces both food intake and body weight (Wynne et al., 2005). As in rats, there is evidence that OXM may also increase energy expenditure in humans (Wynne et al., 2006).

Although OXM has some agonist activity at the glucagon receptor, there is evidence that its anorectic effect is predominantly mediated via the GLP-1 receptor (Baggio et al., 2004; Dakin et al., 2001). The anorectic effects of OXM are abolished in GLP-1 receptor knockout mice (Baggio et al., 2004) and in the presence of the GLP-1 receptor antagonist exendin 9–39 (Dakin et al., 2004), suggesting that OXM acts via the GLP-1 receptor. OXM has a roughly 50-fold lower affinity for the GLP-1 receptor than GLP-1 itself, but despite this, it reduces food intake with similar potency (Dakin et al., 2001). Furthermore, although the administration of exendin 9–39 directly into the ARC blocks the anorectic effects of OXM, it does not block those of GLP-1 (Dakin et al., 2004). Therefore, it is possible that OXM may act via an as yet unidentified receptor or a specific subpopulation of the GLP-1 receptor. Studies using manganese-enhanced magnetic resonance imaging MRI (MEMRI) have shown that intraperitoneal administration of OXM causes a reduced rate of signal enhancement, reflecting a reduction in neuronal activity, in the ARC, PVN, and supraoptic nucleus. This pattern of activation was distinct from that of GLP-1 under the same conditions (Chaudhri et al., 2006), implying that these two hormones act via different hypothalamic pathways.

8. Cholecystokinin (CCK)

CCK is released post-prandially from the small intestine (Murphy and Bloom, 2006), and has also been shown to co-localise with PYY in L cells (Roth et al., 1992). Two types of CCK receptor have been identified in the CNS and peripheral tissues. CCK1 receptors are present in peripheral tissues such as the pancreas, gallbladder, and on vagal afferent nerve fibres innervating the gut (Moran and Kinzig, 2004). Furthermore, CCK1 receptors have been identified in areas within the CNS involved in the regulation of food intake such as the NTS, AP, and dorsomedial hypothalamus (Moran et al., 1986). The CCK2 receptor has a different distribution, and is
found in the cortex, hypothalamus, vagal afferents and gastric mucosa (Moran et al., 1986), once again encompassing several areas known to be involved in appetite regulation.

CCK is released post-prandially in response to saturated fat, long chain fatty acids, amino acids and small peptides that would normally result from protein digestion (Liddel et al., 1985; Rehfeld et al., 2003). CCK release and signalling via the CCK1 receptors in response to these long chain fatty acids mediates stimulation of PYY release and inhibition of ghrelin (an orexigenic gut hormone) in human subjects (Degen et al., 2007). Both of these hormones would then further act to suppress appetite and inhibit food intake. Post-prandial secretion of CCK also triggers the release of pancreatic enzymes, and of bile salts from the gallbladder, into the duodenum, promoting protein and fat digestion (Liddel et al., 1985; Rehfeld et al., 2003). In addition, CCK regulates other gastrointestinal functions including gastric emptying (Fried et al., 1991).

The effects of CCK on appetite are well documented. Peripheral administration of CCK in rodents results in a dose dependant reduction in food intake, decreasing both meal size and duration (Antin et al., 1975). CCK administration is also associated with an increase in post-prandial satiety behaviours such as increased grooming and decreased locomotor activity (Antin et al., 1975). The Otsuka Long-Evans Tokushima Fatty rat was bred to produce a polygenic model of diabetes. These rats lack the CCK1 receptor, are hyperphagic and obese, suggesting that CCK has a physiological role in the regulation of food intake (Bi and Moran, 2002). However, CCK1 receptor knockout mice do not differ significantly in body weight from wild types (Kopin et al., 1999). This discrepancy has been suggested to be due to a number of reasons. The most likely explanation is the potential for the OLETF phenotype to be driven, genetic mutations in addition to the loss of CCK1. These data suggest that CCK may play a role in acute rather than long-term energy homeostasis. It has been reported that endogenous circulating concentrations of CCK cannot activate vagal circuits, suggesting that the actions of CCK on food intake might be paracrine or neurocrine rather than endocrine (Moran, 2000). In humans, intravenous administration of physiological doses of CCK reduces food intake and increases the perception of fullness (Lieverse et al., 1995). Unfortunately, the therapeutic potential of CCK as a treatment for obesity is limited by nausea and tachyphylaxis of the anorectic effects associated with chronic administration (Cowasa et al., 2001).

9. Pancreatic polypeptide (PP)

PP is an amidated 36-amino acid peptide and belongs the ‘PP-fold’ family of peptides. It is released post-prandially under vagal control by pancreatic islet PP cells (Adrian et al., 1976; Larsson et al., 1975; Schwartz et al., 1978). PP is comparable to other anorectic intestinal peptides such as PYY, being secreted in proportion to caloric intake. Circulating levels rise after meals and remain elevated for up to 6 h post-prandially (Adrian et al., 1976).

The functions of PP in regulating gallbladder motility and pancreatic secretions have previously been well characterized (Adrian et al., 1979, 1976; Greenberg et al., 1979). PP has been shown to augment basal insulin and glucagon release in rats and this is thought to be via a direct paracrine effect on the pancreatic beta and alpha cells respectively (Szekowka et al., 1983). Intraperitoneal injection of PP acutely reduces food intake in fasted mice (Asakawa et al., 2003), an effect that remains apparent for 24 h after injection. Furthermore, chronic administration of PP over 6 days in ob/ob mice significantly reduces body weight gain and improves glucose profile (Asakawa et al., 2003). Pancreatic polypeptide-over-expressing mice with supraphysiological PP concentrations have reduced food intake and gain less weight (Ueno et al., 1999).

Intravenous infusion of PP at doses that achieve normal post-prandial plasma concentrations reduces appetite in lean humans and inhibition of food intake persists for 24 h after infusion (Batterham et al., 2003b). PP has also been shown to reduce food intake at lower infusion rates (Jesudason et al., 2007). Furthermore, pancreatic polypeptide has been shown to reduce food intake in patients with obesity secondary to Prader–Willi syndrome (Bernston et al., 1993).

PP has also been implicated in energy homeostasis, with exogenous administration of PP causing an increase in oxygen consumption (Asakawa et al., 2003), thus implying that part of the effect of PP on body weight may be due to increased energy expenditure. It has also been shown to increase spontaneous locomotor activity in mice (Liu et al., 2008).

PP binds to all the members of the Y receptor family, but has the highest affinity for the Y4 receptor subtype (Michel et al., 1998). The effects of PP are likely to be mediated by both the hypothalamus and brainstem (Asakawa et al., 2003). The Y4 receptor mRNA has been shown to be present in the appetite-regulating areas of the brainstem notably the AP and in the ARC (Larsen and Kristensen, 1997; Parker and Herzog, 1995). Functional imaging with MEMRI following peripheral administration of PP has also suggested a central mode of action, demonstrating a significant reduction in signal intensity in the ARC, VMH and PVN of fasted mice. This reduction in signal intensity implies a reduction in activity of neurons in these areas central to the control of appetite. The decrease in signal intensity correlated with a reduction in food intake (Hankir et al., 2011). It has also been suggested that inhibition of food intake by PP may be secondary to an effect on gastric emptying, and therefore increased gastric distension. However, while some investigators have reported an inhibition of gastric emptying, others have failed to show this (Adrian et al., 1981; Batterham et al., 2003b; Schmidt et al., 2005). Furthermore, the anorectic effects of PP in humans appear to be independent of changes in gastric motility (Batterham et al., 2003b). These data have lead to a concerted effort to develop long acting PP analogues, which have completed Phase I trials (Tan et al., 2011).

10. Glucagon

Glucagon is a 29 amino acid peptide secreted from the α-cells of the pancreatic islets of Langerhans. It is a further product of pre-proglucagon cleavage alongside OXM and GLP-1. Glucagon is released into the portal vein in fasted states and also in response to exercise, and acts on the liver to promote hepatic glycogenolysis and gluconeogenesis and maintain glycaemic balance (Stevenson et al., 1987; Striﬄer et al., 1981; Studer et al., 1984; Wasserman et al., 1989).

Glucagon mediates its effects via the glucagon receptor, a 7-transmembrane G protein coupled receptor which has a wide tissue distribution. It is expressed in the gut, adrenal glands, brain, heart, pancreas, spleen and in adipocytes, but is predominantly found in the liver and kidney (Svoboda et al., 1994).

As a potential treatment for obesity, glucagon has been shown to increase energy expenditure in rats, and also in humans during insulin deﬁciency (Davidson et al., 1960; Nair, 1987). It also signiﬁcantly reduces food intake, with a subjective reduction of appetite in man (Schulman et al., 1957). Infusion of glucagon into the portal vein but not the inferior vena cava causes a reduction in meal size in rats (Geary et al., 1993; Le Sauter et al., 1991).

Glucagon presents an interesting prospect in the treatment of obesity due to its effect on increasing energy expenditure, and increasing satiety. It has been demonstrated that the potential unfavourable effect on glucose tolerance due to glucagon’s actions on hepatic glycogenolysis and gluconeogenesis is effectively
counteracted by dual agonism at the glucagon and GLP-1 receptors (Day et al., 2009; Pocai et al., 2009). The data from these studies demonstrated highly effective weight loss in diet-induced obese mice whilst avoiding the hyperglycaemia that might be expected from agonism at the glucagon receptor.

11. Ghrelin

Ghrelin is a 28-amino acid acylated peptide secreted from the stomach. It was originally identified as an endogenous ligand for the ‘growth hormone secretagogue’ receptor (GHS-R) and is a growth-hormone-releasing peptide (Kojima et al., 1999).

Ghrelin is the only orexigenic gut hormone (Bewick et al., 2009), causing an increase in food intake and weight gain in rodents following both peripheral and central administration (Lawrence et al., 2002; Tschop et al., 2000; Wren et al., 2000). Intravenous administration of ghrelin has also been shown to stimulate gastric acid secretion and motility in rats (Masuda et al., 2000). In normal subjects, ghrelin levels are highest in the fasted state (Toshinai et al., 2001), and levels are chronically higher in people with weight loss due to anorexia nervosa or dietary reduction (Ariyasu et al., 2001; Cummings et al., 2002; Shiyi et al., 2002). In contrast to other gut hormones, plasma ghrelin levels decrease after meals (Ariyasu et al., 2001; Tschop et al., 2001) and are low in obese subjects (Shiyi et al., 2002). Ghrelin concentrations are also reduced after gastric bypass surgery, and this may contribute to weight loss in such patients (Cummings et al., 2002).

Ghrelin and its receptor are both expressed in vagal afferents in mice (Page et al., 2007), and blockade of the gastric vagal afferent has been shown to abolish ghrelin-induced feeding, growth hormone secretion, and activation of NPY-producing and growth-hormone-releasing hormone producing neurons in rats (Date et al., 2002). Central administration of ghrelin has been shown to increase pancreatic exocrine secretion via the vagus in conscious rats (Sato et al., 2003).

Ghrelin receptors are found in the ARC of the hypothalamus, and c-fos expression is increased in the ARC after peripheral administration of ghrelin (Hewson and Dickson, 2000). In rodents who had undergone ablation of the ARC, administration of ghrelin did not stimulate food intake (Tamura et al., 2002). When given centrally, ghrelin also stimulates c-fos expression in other nuclei known to be involved in appetite control including the PVN, dorsomedial nucleus, and lateral hypothalamus as well as in the AP and NTS in the brainstem (Lawrence et al., 2002). Hypothalamic levels of orexigenic peptides NPY and AgRP mRNA were also increased after chronic central administration of ghrelin (Kamegai et al., 2001).

Diet-induced obesity is associated with a blunting of ghrelin’s orexigenic effect. There has therefore been recent interest in the interaction between the ghrelin system and macronutrients. High fat feeding has been shown to render NPY/AgRP neurons relatively ghrelin resistant (Briggs et al., 2010), and diets high in fat have been shown to directly inhibit the hyperphagic effect of ghrelin (Gardner et al., 2010; Perez-Tilve et al., 2011). These data have significant implications for developing anti-obesity treatments targeting the ghrelin system and suggest success of these approaches could depend on the fat content of the diet the patient consumes. More recently, ghrelin has been shown to engage neurons in the ventral tegmental area of the brain and may provide a link between the gut and neuronal control of stress-induced eating of ‘comfort foods’ (Chuang et al., 2011).

12. Other gut peptides

A number of other gut-derived peptides have been shown to reduce food intake. However, the physiological role of these peptides in the regulation of food intake and energy homeostasis remains unclear.

NT was first isolated from hypothalamic tissue, but is widely distributed throughout the central nervous system. However, the majority of NT is found within enteroendocrine cells of the GI tract (Carraway and Leeman, 1976). NT regulates a number of digestive processes, including gastrointestinal motility, and pancreatic and biliary secretion (Kitabgi, 2006). It also has trophic effects on the pancreas and small intestine (Feurle et al., 1987; Wood et al., 1988a,b). Plasma levels of NT increase after a meal, with intraluminal fat being the most potent stimulus (Rosell and Rokaeus, 1979). Peripheral administration of neurotensin decreases food intake and grooming behaviour in rats only at large doses (Sandovall and Kulkosky, 1992). Therefore at physiological levels, neurotensin is unlikely to play a major role in appetite regulation. Although neurotensin acutely reduces food intake when administered centrally in rats or peripherally in mice, chronic administration to mice has no significant effect on food intake or body weight (Cooke et al., 2009). The lack of chronic effects on body weight suggests that NT is unlikely to be useful as a treatment for obesity.

Intracerebroventricular injection of glucagon-like peptide-2 (GLP-2) into rats inhibits food intake. In contrast, GLP-2 administered peripherally does not inhibit food intake in rodents. The expression is increased in the ARC after peripheral administration (Hewson and Dickson, 2000). In rodents who had undergone ablation of the ARC, administration of GLP-2 into rats inhibits food intake. In contrast, GLP-2 administered peripherally does not inhibit food intake in rodents. The only currently licensed product in the UK is Orlistat, a pancreatic lipase inhibitor which prevents fat absorption and confers a modest weight loss of 2.9 kg more than placebo over the course of a year (Rucker et al., 2007).

Vasoactive intestinal polypeptide (VIP) has been shown to reduce appetite, in addition to its well-characterized effects on the cardiovascular system and gastrointestinal motility and secretion. Intracerebroventricular administration of VIP has been shown to cause a potent short-lived decrease in food intake and an increase in activity and energy expenditure in rats. Treatment of hypothalamic explants with VIP stimulated the release of the anorexigenic peptide α-MSH (Ghourab et al., 2011). These studies suggest a possible endogenous role for VIP in the hypothalamic control of energy homeostasis.


Lifestyle and dietary modification alone are inadequate for the successful treatment of the majority of obese individuals. However, despite an increasingly high demand for intervention, the field of obesity therapeutics has limited options to offer these patients. The history of obesity pharmacotherapy is littered with examples of drugs withdrawn from the market due to adverse effects outweighing the beneficial effects of weight loss. Recent examples include Sibutramine, a norepinephrine and serotonin reuptake inhibitor, and Rimonabant, which is a cannabinoid-1 receptor blocker. Sibutramine was withdrawn after it was found to increase heart rate and blood pressure in some subjects, and was associated with an increased risk of stroke and non-fatal myocardial infarction in patients with pre-existing cardiovascular conditions (James et al., 2010), whilst Rimonabant was withdrawn amidst concerns regarding adverse psychiatric events (Christensen et al., 2007).
The only obesity treatment that has been shown to confer long-term, sustained weight loss and a decrease in overall mortality is bariatric surgical intervention (Adams et al., 2007; Sjostrom et al., 2007). Several surgical procedures are available to achieve weight loss. Gastric banding restricts the amount of food that can be comfortably ingested and increases the satiating effect of food (Dixon et al., 2005). A more efficient reduction in appetite and weight loss is seen with surgical procedures that involve gastrointestinal bypass, such as Roux-en-Y Gastric bypass (RYGB) (Adams et al., 2007; Kenler et al., 1990; Sjostrom et al., 2007). Weight loss is normally associated with reduced plasma levels of the adipocyte-derived anorectic hormone leptin, causing increased hunger (Chan et al., 2003). However, following RYGB, despite significant reductions in body weight and leptin levels, appetite is markedly reduced (Kenler et al., 1990).

A significant difference in the effects of different forms of bariatric surgery on type 2 diabetes has been shown (Van et al., 2007). RYGB ameliorates coexistent type 2 diabetes mellitus before substantial weight loss has occurred and more rapidly than gastric banding. The differences between gastric banding and RYGB may be due to alterations in the anorectic and incretin gut hormone profile that is seen following RYGB, but not following gastric banding (Kellum et al., 1990; le Roux et al., 2006). Experimental evidence suggests that these anorectic gut hormones may mediate the effects of RYGB on appetite and body weight (le Roux et al., 2006; le Roux et al., 2007). Post-prandial PYY and GLP-1 levels begin to rise as early as 2 days following gastric bypass in humans (le Roux et al., 2007), and secretory products of enteroendocrine L cells, including PYY and GLP-1 remain elevated two years after bypass surgery (le Roux et al., 2010). Inhibiting gut hormone release with somatostatin analogue octreotide increases the food intake after gastric bypass surgery but not following gastric banding (le Roux et al., 2007), further suggesting that these hormones play a critical role. Determining the mechanisms behind this sustained reduction in appetite may identify pathways that can be targeted by anti-obesity agents. To this end there has been recent concerted effort to mimic the rise in gut hormones following gut bypass by either the development of peptide based analogues or by the design of small molecule drugs which target nutrient sensing receptors on the enteroendocrine L cell.

Long acting versions of PYY and OXM are being actively pursued by the pharmaceutical industry, such as Pfizer’s OAP-189, we await the dissemination of data from ongoing trials. Given that gut hormones are co-released one logical approach would be the development of combination therapies. Indeed data suggests that co-administration of gut hormones can have additive effects on food intake inhibition, for example PYY + GLP-1 (Neary et al., 2005) or PYY + OXM (Field et al., 2010). Such combination approaches may prove more effective than individual administration. Very recently the development of chimeric agonists has emerged as a novel form of combination therapy (Day et al., 2009). GLP-1/glucagon co-agonists combine the appetite suppressive effects of GLP-1 and glucagon with the energy expenditure promoting effects of glucagon. Whilst at the same time GLP-1’s insulinotropic effects inhibit the detrimental hyperglycaemic effects of glucagon. Marcadia Ltd., now a subsidiary of Roche, first reported the beneficial effects of this approach and their compound is now undergoing clinical trials. In addition, Zealand Pharma is also developing a similar compound, ZIP-2929, in partnership with Boehringer Mannheim. Time will tell if the promising pre-clinical data translates to in clinical benefit (Daugaard et al., 2010).

Considerable energy has also been directed toward the development of gut hormone secretagogues. The most well characterised class being agonists of GPR119. These compounds have been shown to release both GLP-1 and PYY (Chu et al., 2008). Their anti-diabetic effects are well defined; stimulation of GLP-1 and a direct insulinotropic action (Chu et al., 2007). It is less clear if these compounds will be effective as anti-obesity agents, but some agonists have been shown to significantly reduce food intake, for example PS632408 (Overtorn et al., 2006). GPR119 is currently the only target for which synthetic modulators stimulate both incretin and insulin release. This highly beneficial profile has generated great industry interest with at least 9 companies actively working in this area. Initial clinical trials have been successful with respect to the anti-diabetic indication (Jones et al., 2009; Shah and Kowalski, 2010).

14. Conclusion

Obesity has emerged as a major global healthcare challenge. The significant mortality and morbidity associated with obesity has inspired a vast amount of research directed towards developing safe and efficacious weight loss agents. The beneficial effects of centrally acting weight loss agents have been negated by their potentially hazardous effects on mood, reward, dependence and autonomic tone. Gut hormones, as outlined in this article, play an important role in the homeostatic control of food intake and offer an alternative to centrally acting drugs. In particular, recent data suggests that mimicking the gut hormone profile observed following gastric bypass may offer viable new treatments for obesity. This can be accomplished either through the use of long acting peptide based therapies, alone or in combination, or with gut hormone secretagogues. We believe the most promising avenues for future exploitation lie in the development of longer acting GLP-1 agonists, combination therapies including GLP-1/glucagon co-agonists and gut hormone secretagogues targeting L-cell nutrient receptors (eg. GPR119 agonists) either as small molecules or as functional foods. Thus, our emerging understanding of the physiological systems in the gut which regulate food intake has identified novel targets for the treatment of obesity and its related co-morbidities. We believe that in time these approaches will develop clinically useful compounds which will offer a real answer to the ever growing burden of obesity.

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