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REVIEW

Peripheral neural targets in obesity

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Interest in pharmacological treatments for obesity that act in the brain to reduce appetite has increased exponentially over recent years, but failures of clinical trials and withdrawals due to adverse effects have so far precluded any success. Treatments that do not act within the brain are, in contrast, a neglected area of research and development. This is despite the fact that a vast wealth of molecular mechanisms exists within the gut epithelium and vagal afferent system that could be manipulated to increase satiety. Here we discuss mechano- and chemosensory pathways from the gut involved in appetite suppression, and distinguish between gastric and intestinal vagal afferent pathways in terms of their basic physiology and activation by enteroendocrine factors. Gastric bypass surgery makes use of this system by exposing areas of the intestine to greater nutrient loads resulting in greater satiety hormone release and reduced food intake. A non-surgical approach to this system is preferable for many reasons. This review details where the opportunities may lie for such approaches by describing nutrient-sensing mechanisms throughout the gastrointestinal tract.

Abbreviations

ASIC, acid-sensing ion channel; BMI, body mass index; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; DPP-IV, dipeptidyl peptidase 4; EC, enterochromaffin; FFAR, free fatty acid receptor; GHS, growth hormone secretagogue; GI, gastrointestinal; GIP, glucose-dependent insulinotropic peptide; GLP, glucagon-like peptide; GPRC6A, G-protein-coupled receptor family C group 6 member A; HFD, high-fat diet; mGluR, metabotropic glutamate receptor; NPW, neuropeptide W; PepT1, peptide transporter 1; PYY, peptide tyrosine-tyrosine; T1R, taste receptor subtype 1; TRPM, transient receptor potential channel-melastatin subtype; TRPV, transient receptor potential channel-vanilloid subtype; WHO, World Health Organization

Introduction

Obesity is a major health issue in the modern era, with its increasing prevalence focussing attention on a problem not of famine or infection, but the outcome of surplus. Most developed societies are experiencing an epidemic of obesity and its closely related co-morbidity type 2 diabetes (Chan *et al.*, 1994; Colditz *et al.*, 1995). The prevalence of obesity worldwide has more than doubled since 1980, with 2.6 million deaths directly related to the disease *each year* and predictions that by 2015, over 1.5 billion adults will be overweight [body mass index (BMI) >25] or obese [BMI >30, World Health Organization (WHO) 2011]. Obesity further contributes to increased incidence of diseases such as ischaemic heart disease, stroke, hypertension, obstructive sleep apnoea, non-alcoholic steatohepatitis, polycystic ovary syndrome and numerous forms of cancer (Calle *et al.*, 2003; Ning *et al.*, 2010). Although being overweight or obese is a serious risk to both physical and mental health, it is extremely resistant to behavioural intervention (Wadden *et al.*, 2004). Very recent evidence suggests that increased drive to eat upon dieting is a result of decreased gut hormone release, rather than being entirely a psychological phenomenon (Sumithran *et al.*, 2011). To date, therapeutic approaches to obesity management have been largely aimed at appetite control via actions within the CNS, and have had limited efficacy and/or unacceptable adverse effects. Probably, the most effective current interventions in obesity are firstly, gastric bypass surgery, whereby nutrient is shunted to distal regions of the intestine, where it provokes greater release of satiety hormones via a

chemosensory mechanism (Bueter and le Roux, 2011), although intestinal bypass procedures improve glucose homeostasis disproportionately to weight loss (Rubino *et al.*, 2010), indicating there are additional consequences of this surgery besides satiety. The second major intervention is gastric banding, which restricts the volume that can be contained within the stomach before it becomes overstretched and excessively activates mechanosensory nerves. These treatments have their own drawbacks that are beyond the scope of this review, but they exemplify the potential of peripherally directed approaches to obesity. Not surprisingly, there is growing interest in developing non-surgical, pharmacological therapies that lead to a reduction in energy intake by altering satiety and/or hunger and, thereby, weight loss. Targeting the initiation of the satiety signal arising from the gastrointestinal (GI) tract is, therefore, an attractive therapeutic treatment for obesity.

Pathways from the gut involved in appetite suppression

Satiation following food intake occurs via two principal routes within the GI tract – distension of the stomach, and the release of GI peptides in response to the presence of luminal nutrients. Table 1 shows the range of nutrient receptors that are thought to be expressed on gut epithelial cells and elsewhere. From this, it is clear that there is the capacity for detection of all major classes of nutrients, and discrimination according to specific molecular variants of amino acids and fatty acids. Many of these nutrient receptors are GPCR, and mirror a role they may have elsewhere in the body. For example, the calcium-sensing receptor functions to detect both amino acids and extracellular calcium concentrations, which is crucial in parathyroid function, but also in gastric hormone release (see later Buchan *et al.*, 2001). In some cases, specific GPCR are co-localized with specific hormones (Hirasawa *et al.*, 2005), but on the whole, the organization of this system is poorly understood, and the relative role of each type of receptor is unclear. There are some parallels with the taste system that operates in the lingual epithelium, and many components of this pathway are found in the gut. In particular, sweet taste receptors are coupled via the G-protein α-gustducin, and via PLCβ, lead to opening of the transient receptor potential channel transient receptor potential channel-melastatin subtype (TRPM)5, which in turn allows calcium influx and excitation and secretion of mediators such as glucagon-like peptide-1 (GLP-1, see later).

While hormones released from GI tract can signal satiety directly to the CNS, strong functional evidence exists to show that vagal afferent neurons are a primary route to convey mechanical and chemical cues from the GI tract to the brainstem and higher brain centres. Within these brain regions, gustatory, olfactory and textural inputs are then integrated with past experience to control feeding behaviour (Broberger and Hokfelt, 2001; French and Cecil, 2001).

While outside the focus of this review, the role of spinal sensory afferents in food intake regulation is less well known. Spinal sensory innervation of the GI tract is thought to be mainly involved in signalling pain in response to potentially injurious stimuli such as acid-pepsin attack, over-distension or spasm. The cell bodies of gastric and intestinal spinal afferents reside mainly in the thoracic and lumbar dorsal root ganglia adjacent to the spinal cord. Recordings from these afferent pathways show that responses to nutrients do occur (Ranieri *et al.*, 1973; Perrin *et al.*, 1981; Mei *et al.*, 1984); however, evidence so far suggests their role in food intake regulation is minor. For example, bilateral abdominal splanchnectomy in rats does not lead to significant weight loss, in comparison to vagotomy (Furness *et al.*, 2001). Celiac-superior mesenteric ganglionectomy, however, has been shown to reduce acute intake during intraduodenal carbohydrate or fatty acid infusion in rats, while a role of splanchnic afferents in conveying gastric mechanical signals has been suggested (Ozaki and Gebhart, 2001; Sclafani *et al.*, 2003). Further experiments are required to determine the exact contribution of spinal afferents to the GI satiety signal, and whether these afferents signal this directly, and/or indirectly (for example, via mediating changes in intestinal blood supply).

Vagal sensory innervation of the GI tract arises from afferent neurones with cell bodies in the nodose and jugular ganglia, and with endings concentrated in the upper GI tract. Nerve tracing studies have shown that vagal afferent nerves terminate within the muscular layers of the GI tract, within the mucosa, or at both sites. Mechanically sensitive vagal afferent endings form specialized endings within the muscularis externae associated with myenteric ganglia as intraganglionic laminar endings (tension receptors) or as in series intramuscular arrays (putative stretch receptors) running in parallel to circular or longitudinal muscle fibres (Neuhuber, 1987; Berthoud *et al.*, 1992; Zagorodnyuk *et al.*, 2001; Powley and Phillips, 2011). Mucosal vagal afferents (mucosal receptors), in contrast, terminate within the parenchyma of mucosal villi in close contact with the basal lamina, but not with the epithelial surface (Berthoud *et al.*, 1995) and are both mechanosensitive and chemosensitive. This anatomy largely precludes a direct chemosensory action by luminal stimuli, and indicates that specialized epithelial cells serve as primary GI chemosensory cells, and signal to adjacent vagal afferent endings, or enteric neurons, in a paracrine manner. These specialized cells represent less than 1% of the mucosal cell population but together form the largest endocrine organ of the body. They are regionally distributed throughout the GI tract and possess an array of transduction machinery to sense luminal stimuli, and in turn, release over 20 different gut peptides or bioactive molecules (for review, see Cummings and Overduin, 2007; Rindi *et al.*, 2004). Many of these gut peptides undergo rapid proteolytic breakdown in circulation or have high liver clearance, indicating that physiological effects beyond their site of local release within the lamina propria may be limited. Accordingly, paracrine activation of vagal afferent endings is likely to represent an important mode of satiety signalling.

Gastric vagal afferent satiety signals

Investigations of the role in satiety of vagal afferents innervating the stomach have generally been conducted by disruption of the vagal innervation to all abdominal viscera, but

Table 1

Ligand, location and GI mediators associated with nutrient-sensing receptors

	Ligand	Location	GI mediators	Reference
Carbohydrate, sweet sensing				
T1R2/T1R3 (Tas1r2/Tas1r3)	Sweet tastants: glucose, fructose, sucrose, D-amino acids[1,2] Sweeteners: aspartame, dulcin cyclamate, saccharin, ace-sulfame K[1,2]	Taste buds[2] GI tract: jejunum, ileum, colon[3,4] Brain [5] Pancreas [6]	T1R2: GIP[7], CCK[8], GLP-1[9] (PYY [10]) T1R3: GIP[7], GLP-1[7], ghrelin[11] (PYY[12])	[1](Li *et al.*, 2002), [2](Nelson *et al.*, 2001), [3](Bezencon *et al.*, 2007), [4](Dyer *et al.*, 2005), [5](Ren *et al.*, 2009), [6](Nakagawa *et al.*, 2009), [7](Moran *et al.*, 2010a), [8](Shen *et al.*, 2005), [9](Moran *et al.*, 2010b), [10](Gerspach *et al.*, 2011), [11](Hass *et al.*, 2010), [12](Steinert and Beglinger, 2011)
Protein hydolysate, amino acid sensing				
GPR93 (GPR92/Lpar5)	Protein hydrolysate, oleoyl-L-α-lysophosphatidic acid[13] farnesyl pyrophosphate N-arachidonylglycine[14]	GI tract: stomach, small intestine, large intestine[13] Lymphocytes[15] Brain[13,15]	CCK[16]	[13](Choi *et al.*, 2007a), [14](Oh *et al.*, 2008), [15](Kotarsky *et al.*, 2006), [16](Choi *et al.*, 2007b)
mGluR1	Agonist potency: quisqualate >3,5-dihydroxyphenylglycine = glutamate > > (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid >3-hydroxyphenylglycine; glutamate acts as a full agonist, others as partial agonists[17,18]	Taste buds (circumvallate)[19] GI tract: fundic glands, duodenal mucosa, ileum[20–22] Brain[22,23,24,25]	Not assessed with GI mediators	[17](Schoepp *et al.*, 1994), [18](Aramori and Nakanishi, 1992), [19](Toyono *et al.*, 2003), [20](Akiba *et al.*, 2009), [21](San Gabriel *et al.*, 2007), [22](Martin *et al.*, 1992), [23](Testa *et al.*, 1994), [24](Görcs *et al.*, 1993), [25](Stephan *et al.*, 1996)
mGluR4	Agonist potency: L-2-amino-4-phosphonobutyrate (L-AP4) > L-serine-O-phosphate [26] > L-glutamate > (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid > > quisqualate > quisqualate > L-homocysteate = ibotenate[27,28]	Taste buds[29] GI tract: fundic and duodenal mucosa[20,30] Brain[28,31,32,33] Nodose ganglia[33]	Not assessed with GI mediators	[26](Thomsen and Suzdak, 1993), [27](Kristensen *et al.*, 1993), [28](Flor *et al.*, 1995), [29](Chaudhari *et al.*, 1996), [30](Chang *et al.*, 2005), [31](Tanabe *et al.*, 1993), [32](Makoff *et al.*, 1996), [33](Hoang and Hay, 2001)
Calcium-sensing receptor (CasR)	L-amino acids (preference for aromatic and aliphatic amino acids)[34]	Taste buds[35] GI tract: oesophagus[36], fundic glands[20,37,38], duodenal mucosa [20], ileum[39], colon[40] Brain[39,41]	Gastrin[42], CCK[43]	[34](Conigrave *et al.*, 2000), [35](Bystrova *et al.*, 2010), [36](Justinich *et al.*, 2008), [37](Dufner *et al.*, 2005), [38](Haid *et al.*, 2011), [39](Ruat *et al.*, 1995), [40](Chihara *et al.*, 1979), [41](Ferry *et al.*, 2000), [42](Ray *et al.*, 1997), [43](Wang *et al.*, 2011)
T1R1/T1R3 (Tas1r1/Tas1r3)	Most amino acids (notably l-aspartate and l-glutamate), but not their D-enantiomers or other compounds[44]	Taste buds (fungiform)[45] GI tract: oesophageal mucosa[20], gastric mucosa/antrum[3,20], duodenal mucosa[3,20], jejunum[3,46], ileum[3], colon[3] Brain[5] Sensory neurons[20]	T1R1: NA T1R3: See above	[44](Nelson *et al.*, 2002), [45](Raliou *et al.*, 2009), [46](Mace *et al.*, 2007)
GPRC6A	Basic L-alpha-amino acids L-Arginine, L-Lysine, L-ornithine[47]	Taste cells[35] Stomach[38] Brain [48,49]	Gastrin[38]	[47](Wellendorph *et al.*, 2005), [48](Wellendorph and Bräuner-Osborne, 2004), [49](Luo *et al.*, 2010)

Table 1

Continued

	Ligand	Location	GI mediators	Reference
Fatty acid sensing				
GPR41 (FFAR3)	Agonist potency: Propionate = pentanoate = butyrate > acetate > formate[50]	Colonic mucosa[51] Brain[52]	CCK[53], PYY[51] (leptin[54])	[50](Brown *et al.*, 2003), [51](Tazoe *et al.*, 2009), [52](Bonini *et al.*, 1997), [53](Samuel *et al.*, 2008), [54](Xiong *et al.*, 2004)
GPR43 (FFAR2)	Agonist potency: Acetate = propionate = butyrate > pentanoate > hexanoate = formate > valerate[50,55]	Oral tissue[56] GI tract: ileum[57], colon[57,58])	PYY[57], GLP-1[59] (PYY[60])	[55](Nilsson *et al.*, 2003), [56](Mau *et al.*, 2011), [57](Karaki *et al.*, 2006), [58](Karaki *et al.*, 2006), [59](Kaji *et al.*, 2011), [60](Zaibi *et al.*, 2010)
GPR84	Medium-chain fatty acids with acyl chain lengths 9–14. Agonist potency: Capric acid (C10) > Undecanoic acid (C11) > Lauric acid (dodecanoic acid) (C12) > Tridecanoic acid (C13) > Myristic acid (C14) > Nonanoic acid (C9) [61]	Not assessed in GI, vagal pathways	Not assessed with GI mediators	[61](Wang *et al.*, 2006)
GPR40 (FFAR1)	Medium- and long-chain saturated and unsaturated fatty acids[62]. Medium-length saturated fatty acids (C10–12) have the highest potency: Capric acid > lauric acid > myristic acid > palmitic acid. Unsaturated free fatty acids with C < 20 carbon atoms activate, but with lower potency Stearidonic acid > linolenic acid > linoleic acid > oleic acid)[63]	Taste buds[64] GI tract: pylorus, duodenum, jejunum, ileum, colon[65] Brain[62,66]	Gastrin, GIP, CCK, PYY, GLP-1, ghrelin[65]	[62](Briscoe *et al.*, 2003), [63](Kotarsky *et al.*, 2003), [64](Cartoni *et al.*, 2010), [65](Edfalk *et al.*, 2008), [66](Ma *et al.*, 2007)
GPR120	Long-chain unsaturated fatty acids α-Linolenic acid (C18:3) > γ-Linolenic acid (C18:3) > cis-11,14,17-Eicosatrienoic acid (C20:3) > cis-5,8,11,14,17-Eicosapentaenoic acid (C20:5) > Palmitoleic acid (C16:1) > cis-4,7,10,13,16,19-Docosahexaenoic acid (C22:6)[67,68]	Taste buds (circumvallate)[64,69] GI tract: stomach[70], small intestine[12,67], colon[71]	GIP[72], CCK[73], GLP-1[71]	[67](Hirasawa *et al.*, 2005), [68](Burns and Moniri, 2010), [69](Matsumura *et al.*, 2007), [70](Fredriksson *et al.*, 2003), [71](Miyauchi *et al.*, 2009), [72](Parker *et al.*, 2009), [73](Tanaka *et al.*, 2007)
GPR119	Lysophosphatidylcholine[74], oleoylethanolamide[75], endovallinoid N-oleoyldopamine[76], 2-oleoyl glycerol and 2-monoacylglycerols[77]	GI tract[75] Brain[75]	GIP[72], PYY[78] (GLP-1[79])	[74](Soga *et al.*, 2005), [75](Overton *et al.*, 2006), [76](Chu *et al.*, 2010), [77](Hansen *et al.*, 2011), [78](Sakamoto *et al.*, 2006), [79](Flock *et al.*, 2011)

The majority of localization data listed is from immunohistochemistry studies in rodents and humans. Bracketed GI mediators indicate a functional association between receptor and GI hormone exists (e.g. GI hormone release upon agonist activation), but direct co-localization has not been established.

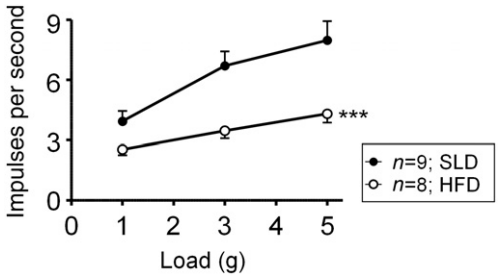

Figure 1

Response of gastric tension receptors to circular stretch in mice fed either a standard laboratory diet (SLD; 7% energy from fat) or a HFD (60% energy from fat). The response to stretch is significantly reduced in mice fed a HFD ($P < 0.00$; two-way ANOVA). From Kentish *et al.* (2011).

this unfortunately provides no discrete evidence of the contribution of gastric vagal afferents (for review, see Ritter, 2004). However, disruption of vagal pathways in rodents with closed pyloric cuffs (to prevent post-gastric-mediated satiation) led to increased consumption and attenuated the reduction of food intake following gastric preloads (Lorenz, 1983). These data highlight a distinct role of gastric vagal afferents in satiety signalling. In humans, there are two main surgical approaches to obesity, both of which involve reduction in the size of the stomach. One is gastric reduction alone, whereby the volume of the stomach is reduced by resection or using an extraluminal band; the other is by gastric resection combined with bypass of a large part of the small intestine. Both types of surgery are effective treatments for obesity, which argues in favour of approaches that target the gastric satiety signal (Elder and Wolfe, 2007). Gastric restriction is accomplished by creating a small gastric pouch and restricting gastric emptying by reducing the size of the gastric outlet, inducing early satiety presumably by increased activation of gastric mechanoreceptors. Other mechanisms of action of bariatric surgery include malabsorption. However, after bariatric surgery, 80% of weight loss is achieved due to diminished energy intake rather than malabsorption (Elder and Wolfe, 2007); therefore, gastric restriction alone is effective in obesity control. The consequence of reducing the size of the stomach is that a smaller meal volume is able to exert sufficient mechanical stimulus to activate vagal mechanoreceptive afferents (Blackshaw *et al.*, 1987), which signal fullness to the CNS. Correspondingly, vagal electrical stimulation has been shown to reduce food intake and body weight in rats (Laskiewicz *et al.*, 2003) and more specifically, electrical modulation of gastric vagal nerves is being used successfully for the treatment of obesity in humans (Toouli *et al.*, 2007). Gastric bypass surgery provides an additional mechanism to gastric restriction, by direct exposure of the distal small intestine to unabsorbed nutrient, which activates intestinal chemosensory mechanisms (see later).

There are two functional classes of mechanosensitive vagal afferents in the stomach, mucosal receptors and tension receptors, according to the location of their mechanoreceptive fields (examples in Figures 1 and 3; Iggo, 1955; 1958; Davison, 1972; Clarke and Davison, 1975; Cottrell and Iggo, 1984a,b; Page and Blackshaw, 1998; Page *et al.*, 2002). Both of these classes give rise to behavioural changes when activated.

We have shown that mucosal receptors are generally silent at rest and respond mechanically to light stroking of the mucosa, generating a burst of action potentials each time the stimulus passes over the receptive field (Page and Blackshaw, 1998; Page *et al.*, 2002). They are insensitive to distension and contraction of the gastric wall. There is evidence that they are important in the initiation of satiety, nausea and vomiting by chemical and osmotic stimuli (Andrews and Sanger, 2002). In the stomach, solid food is triturated into small particles before emptying into the duodenum. Mucosal afferents in the antrum and pylorus are the most likely to mediate this discrimination of particle size and provide negative feedback onto control of gastric motor patterns that promote emptying (Becker and Kelly, 1983; McIntyre *et al.*, 1997; Tuleu *et al.*, 1999). Their high sensitivity to mechanical stimulation of the mucosa also makes them ideal candidates for detecting undigested food to initiate satiety signals.

Tension receptors often have a resting discharge that may be modulated in phase with ongoing contractions. They show slowly adapting responses to normal contractions and distension with a linear relationship to wall tension (Blackshaw *et al.*, 1987; Page and Blackshaw, 1998; Page *et al.*, 2002). Tension receptors signal the level of gastric distension to the CNS, which is important not only in triggering reflexes controlling GI function, but also critical in signalling food intake and generating sensations such as satiety and fullness. Because of their exquisite sensitivity to distension, their signalling of an isovolumetric load is amplified after formation of a gastric pouch (Blackshaw *et al.*, 1987; Blackshaw and Grundy, 1989), as occurs in bariatric surgery, providing a markedly increased satiety signal. We have recently reported that the mechanosensitivity of gastric vagal afferent tension receptors is significantly reduced after chronic consumption of a high-fat diet (HFD) suggesting that the satiety signal would be reduced in these circumstances (see (Kentish *et al.*, 2011; Figure 1). Such a mechanism may have evolved to maximize assimilation of energy from calorie-rich foods in anticipation of famine. A number of studies have shown that obese humans have increased gastric capacity (Geliebter, 1988; Kim *et al.*, 2001), which would result in increased energy intake. This could occur due to a reduction in the gastric distension-stimulated vagal afferent satiety signal. Another recent study has shown that the sensitivity of jejunal afferents to satiety stimuli is also reduced after a HFD (Daly *et al.*, 2011). They revealed that the major mechanism for this decrease in sensitivity is a reduction in the excitability of the neuronal cell membrane (Daly *et al.*, 2011). An alteration in the ion channels involved in mechanotransduction may explain this reduction in excitability of vagal afferents. For example, transient receptor potential vanilloid type-1 (TRPV1) channels have been implicated in obesity. Capsaicin activation of TRPV1 channels has been shown to prevent obesity, while the relative expression of TRPV1 in visceral adipose tissue was significantly reduced in mice fed with a HFD (Zhang *et al.*, 2007). In addition, researchers have shown that consumption of red pepper (a source of capsaicin) along with caffeine significantly reduced energy intake in humans (Yoshioka *et al.*, 2001). Therefore, it is possible that the reduction in mechanosensitivity of tension receptors is due to an

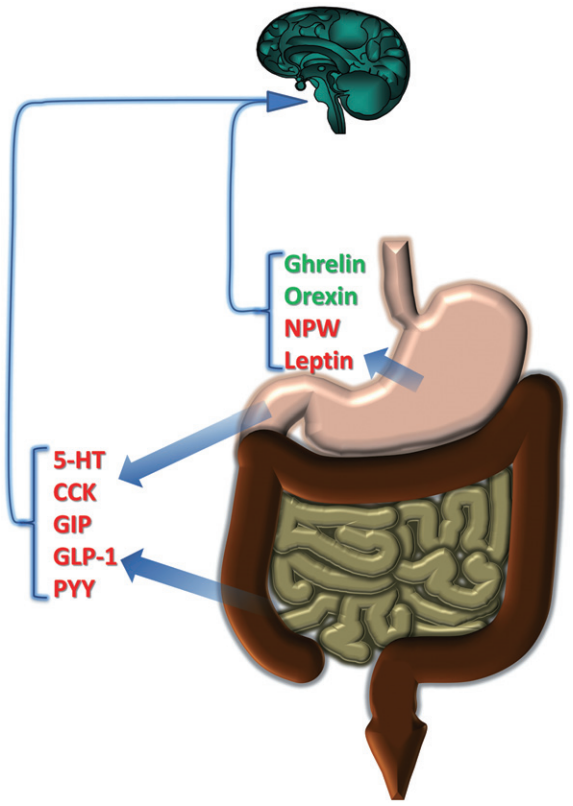

Figure 2

Release of mediators from different regions and effects on food intake. Red indicates inhibition of food intake; green is promotion. Although many mediators act via vagal pathways, some may instead/in addition directly in the brain. See text for details.

alteration in the expression of TRPV1 channels in these particular vagal afferent neurones. However, acid-sensing ion channels (ASIC3s) have also been implicated in gastro-oesophageal vagal afferent mechanosensitivity (Page *et al.*, 2005) and therefore further research in this area is required to find the mechanism responsible for the reduction in mechanosensitivity after chronic consumption of a HFD.

Gastric mechanosensitive vagal afferents can also be modulated by peptides or hormones known to affect appetite. In fact, many of these peptides have been shown to be located in gastric epithelial cells and are therefore in an ideal position to be released and act upon local gastric vagal afferent endings.

Gastric hormones have been shown to have potent effects on satiety, and there is an abundance of evidence that this occurs via vagal mechanisms (Date *et al.*, 2002; Peters *et al.*, 2005). A rich variety of hormones are released from the epithelium of which numerous are implicated in the role of satiety signalling. Their role, source and targets are detailed below and in Figure 2.

Leptin

Traditionally, it was thought that only leptin released from adipocytes was responsible for the long-term regulation of food intake. However, in addition to its role as an adipocytic mediator, leptin is also a gut peptide that interacts with vagal afferents. Epithelial cells in the stomach synthesize and secrete leptin in rodents (Bado *et al.*, 1998) and in humans (Sobhani *et al.*, 2000). Leptin-secreting cells in the epithelium were initially identified as pepsinogen-secreting chief cells (Bado *et al.*, 1998; Sobhani *et al.*, 2000); however, subsequent studies have also detected leptin in the secretory granules of endocrine P cells in the gastric fundus and pylorus (Cinti *et al.*, 2000). Leptin release from the stomach is regulated by feeding (Attoub *et al.*, 1999) (although which nutrients are responsible is unknown), acetylcholine released by the vagus nerve (Sobhani *et al.*, 2002) and small intestinal hormones such as cholecystokinin (CCK) and secretin (Bado *et al.*, 1998; Sobhani *et al.*, 2000). Cell bodies of abdominal vagal afferents in the nodose ganglia synthesize receptors and transmitters, which are subsequently transported to the nerve terminals (Figure 3). Expression of leptin receptor mRNA has been detected in both rodent and human nodose ganglia (Buyse *et al.*, 2001; Burdyga *et al.*, 2002), while vagal afferent neurons possess functionally active leptin receptors (Buyse *et al.*, 2001).

Ghrelin

This orexigenic (appetite-stimulating) signal from the stomach is an endogenous ligand for the growth hormone secretagogue (GHS) receptor (Inui, 2001; Date *et al.*, 2002). Ghrelin has been shown to be located exclusively in endocrine X/A-cells (now designated Gr cells), with the highest concentrations found in the oxyntic glands of the gastric fundus and to a lesser extent the gastric antrum (Date *et al.*, 2000). Ghrelin is secreted from gastric endocrine cells into the circulation, and while the exact stimulus for ghrelin release is not known, there are many stimuli that can inhibit the process. At least part of ghrelin signalling from the stomach is mediated via an ascending neural network through the vagus nerve and brainstem nuclei that ultimately reaches the hypothalamus (Asakawa *et al.*, 2001; Date *et al.*, 2002). We have shown that peripheral vagal afferent endings in the stomach are found in close apposition to ghrelin containing epithelial cells (Kentish *et al.*, 2011) GHS receptors are localized to vagal afferents that project to the rat stomach and we have shown GHS receptor expression in the mouse nodose ganglia (Page *et al.*, 2007). There is some controversy around the role of the vagus nerve in the orexic effects of ghrelin. Date and colleagues (Date *et al.*, 2002) showed that either truncal or selective gastric vagotomy or perivagal capsaicin abolished the action of ghrelin when given intravenously in rats. Findings of Asakawa and colleagues (Asakawa *et al.*, 2001) support this view, showing that ghrelin inhibits the resting discharge in whole vagal nerve recordings and that lesioning vagal afferent fibres inhibits the appetite-stimulating actions of ghrelin. In contrast, Arnold and colleagues (Arnold *et al.*, 2006) showed no effect of vagotomy on the acute effects of ghrelin administered intraperitoneally. We have reported that ghrelin inhibits the mechanosensitivity of gastric tension receptors but not mucosal receptors (Page *et al.*, 2007). After chronic consumption of a HFD or acute food restriction, this selective inhibition of gastric tension receptors is extended to include gastric mucosal receptors (Kentish *et al.*, 2011). Since gastric mucosal receptors are considered to be important in detecting particulate

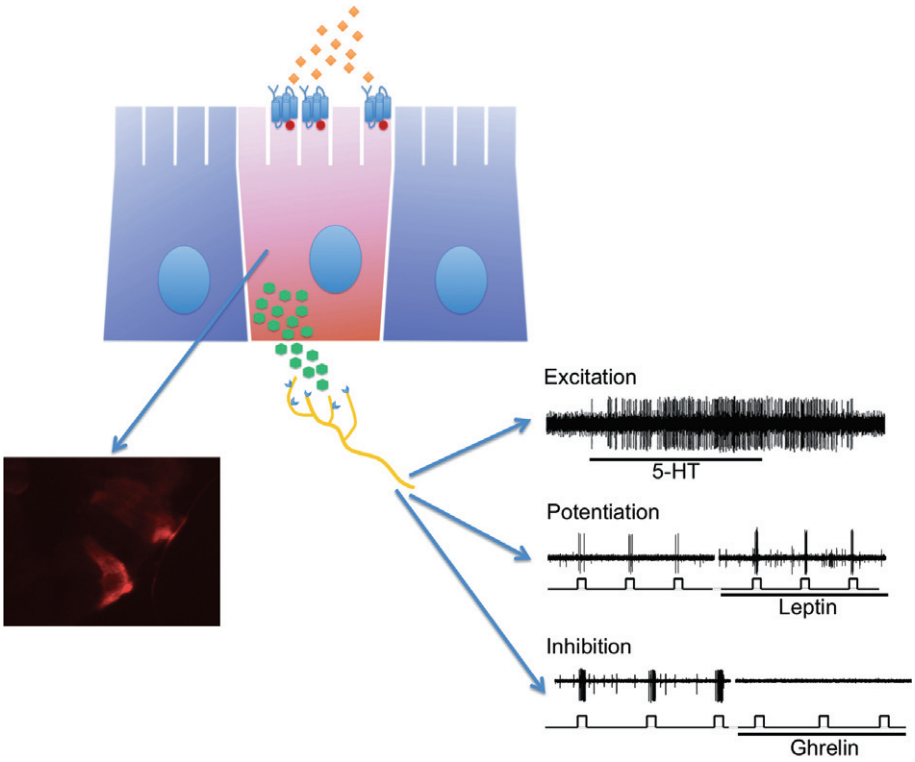

Figure 3

Release mechanism and activation of enteroendocrine cells. Nutrient (diamonds) activate GPCR (blue) on enteroendocrine cell (pink), which via G-proteins (red) activate mediator release on to receptors (blue) on vagal afferents (yellow). Fluorescence micrograph inset shows cell in human colonic epithelium activated *in vitro* by lauric acid [phosphorylated extracellular-regulated kinase (pERK) immunohistochemistry, unpublished], Nerve recording insets show direct and modulatory effects on vagal afferents of released mediators. Data from Page *et al.* (2002), Kentish *et al.* (2011) and unpublished. Recordings are from gastric mucosal afferents in mice. Square waves indicate timing of mechanical stimuli. Note that ghrelin is probably constitutively released rather than induced by nutrient receptors.

content, which reduces gastric emptying and food intake (McIntyre *et al.*, 1997; Tuleu *et al.*, 1999), ghrelin is likely to reduce this satiety signal during fasting and in obesity. In fasted healthy volunteers, ghrelin administration has been shown to increase the rate of gastric emptying in addition to elevating hunger ratings (Falken *et al.*, 2010); this may be a consequence of the decreased mechanosensitivity of gastric mucosal receptors by ghrelin. Together, these data indicate marked plasticity in the mechanism of action of ghrelin under different feeding states.

Neuropeptide W (NPW)

Neuropeptide W is a recently discovered peptide that activates the orphan G-protein-coupled receptors GPR7 and GPR8 (Tanaka *et al.*, 2003). NPW has been suggested to exert a modulatory role in the control of food intake in the brain since central administration of human NPW in rats stimulated food intake (Shimomura *et al.*, 2002; Levine *et al.*, 2005). However, NPW has also been shown to be present in antral epithelial gastrin (G) cells of rat, mouse and human stomach (Mondal *et al.*, 2006). It is known that these cells respond to dietary amino acids via the G-protein-coupled calcium sensing receptor, which induces excitation via phospholipase C (Buchan *et al.*, 2001). Gastric mucosal expression of NPW mRNA in fasted or food restricted animal models is reduced and normalized upon refeeding (Caminos *et al.*, 2008). In addition, GPR7 knockout mice were shown to be hyperphagic and became obese (Ishii *et al.*, 2003). Together, this suggests an anorectic role for gastric NPW (Mondal *et al.*, 2003). However, preliminary studies within our laboratory indicate that NPW reduces the mechanosensitivity of gastric vagal afferents and thus, like ghrelin, has a peripheral orexigenic effect (Li *et al.*, 2011). This NPW-induced reduction in vagal afferent mechanosensitivity is lost after chronic consumption of a HFD (Li *et al.*, 2011) possibly as a protective mechanism as a result of an energy imbalance.

Orexin

Orexins are neuropeptides first localized in neurons within the lateral hypothalamus (Nambu *et al.*, 1999; Takahashi *et al.*, 1999). They are involved in feeding behaviour by stimulating appetite and food consumption (Wolf, 1998). Two types of orexins have been identified, orexin A and B (Sakurai *et al.*, 1998), derived from a common precursor. Early reports suggested that orexins were restricted to the hypothalamus, however, subsequently, it has been shown that a subset of neurons and endocrine cells of the GI tract also contain orexin A and express functional receptors (Kirchgess-

ner and Liu, 1999). Orexin A immunoreactivity has been found in endocrine cells in gastric pyloric glands of rodents, where a subset co-localizes with gastrin, in addition to endocrine cells in the human stomach (Kirchgessner and Liu, 1999; De Miguel and Burrell, 2002; Nakabayashi *et al.*, 2003). Orexin-1 receptor has also been localized in vagal afferent neurons of humans and rats, while orexin A has been shown to inhibit jejunal vagal afferent responses to CCK (see later Burdyga *et al.*, 2003; 2010). Although not directly investigated, it is possible that orexin A released from gastric endocrine cells could modulate the response of gastric vagal afferents to mechanical stimulation, thereby influencing gastric vagal afferent signalling of satiety.

Non-peptide transmitters such as endocannabinoids and nitric oxide have also been implicated in satiety signalling. There is substantial evidence for the role of nitric oxide in feeding behaviour in the hypothalamus (Czech, 1996; Yamada *et al.*, 1996; Czech, 1998; Czech *et al.*, 1998; Calapai *et al.*, 1999; Morley *et al.*, 1999) but little is known about its role in satiety signalling in the periphery. Studies have shown that nitric oxide is important in the actions of many appetite control peptides including ghrelin, neuropeptide Y, orexin A and leptin (Morley *et al.*, 1999; Gaskin *et al.*, 2003; Farr *et al.*, 2005). For example, the effect of the peptides CCK, neuropeptide Y and ghrelin on food intake is lacking in nitric oxide synthase knockout mice (Morley *et al.*, 2011). Indeed, we have recently reported a role for endogenous nitric oxide as a peripheral modulator of gastro-oesophageal sensory function (Page *et al.*, 2009). Nitric oxide synthase containing cells located within the gastric mucosa are an endogenous source of nitric oxide, which are in close proximity to vagal afferent endings (Page *et al.*, 2009). Therefore, there is a peripheral nitric oxide-vagal afferent pathway that may be involved in appetite regulation. Preliminary data from our laboratory further indicate that there is a switch in the effect of endogenous nitric oxide on vagal afferent mechanosensitivity – from inhibitory in fed animals to excitatory in fasted animals (Elliott *et al.*, 2011). This switch is due to signal transduction via alternate second messenger pathways in response to nitric oxide.

Intestinal vagal afferent satiety signals

The intestine, the major site of macronutrient breakdown and nutrient absorption, is extensively innervated by vagal afferents with peak density in the duodenum and lower density in the ileum and distal intestine (Jagger *et al.*, 1997). Intestinal vagal afferents that terminate within muscle layers are directly responsive to mechanical stimuli (Clarke and Davison, 1978), similar to those innervating muscle layers of the stomach. Mucosal vagal afferents, however, are likely to respond directly to chemical signals from primary sense cells within the intestinal mucosa (Figure 3). In support of a paracrine action of enteroendocrine cells, subsets of intestinal vagal afferents are known to express receptors for a number of key hormones released by gut epithelial cells, including those released in response to luminal nutrients (Kakei *et al.*, 2002; Raybould *et al.*, 2003; Nakagawa *et al.*, 2004; Vahl *et al.*, 2007; Bucinskaite *et al.*, 2009); a number of these important signal mediators are discussed below.

Intestinal vagal afferents are responsive to a wide array of luminal stimuli, including hyperosmotic and hypo-osmotic solutions, acids and bases, and breakdown products of carbohydrates, proteins and fats (Clarke and Davison, 1978; Mei, 1978; Mei and Garnier, 1986; Lal *et al.*, 2001). Intestinal perfusion with water, for example, has been shown to specifically activate subsets of intestinal vagal afferents in cats and rats (Mei and Garnier, 1986; Zhu *et al.*, 2001). Infusions of hyperosmotic solutions exceeding 500 mosM also directly activate nodose ganglion neurons in rats, and significantly inhibit food intake in pigs (Houpt *et al.*, 1983; Zhu *et al.*, 2001). This osmolarity is within the normal postprandial range of ingesta within the intestine and indicates that non-nutritive characteristics of ingesta contribute to the intestinal satiety signal, and signal largely via vagal pathways. Intestinal nutrients exert powerful effects on food intake and satiety via vagal pathways. Subdiaphragmatic vagotomy or abdominal afferent denervation using the neurotoxin capsaicin largely or completely blocks the inhibition of food intake following intestinal infusion of carbohydrates or fatty acids (Yox and Ritter, 1988; Walls *et al.*, 1995). Correspondingly, expression of the immediate early gene product, c-fos, in vagal brainstem nuclei, closely follows intraduodenal infusion of these nutrients (Phifer and Berthoud, 1998). Together, these data highlight the critical role of intestinal vagus signals in satiety, and the rationale of targeting the vagus in managing obesity. There are also many examples of intestinal nutrient infusion slowing gastric emptying via vagal reflex pathways in animals and humans (Wilkinson and Johnston, 1973; Roze *et al.*, 1977; Raybould and Holzer, 1992; Schwartz *et al.*, 1993). In healthy humans, this rate is slowed to 1–3 kcal·min^{-1}, a rate matched to the absorptive capacity of the small intestine (Brener *et al.*, 1983; Raybould, 1998). However, it is important to appreciate that while slowing of gastric emptying may interact with intestinal satiety signalling, the suppression of food intake by intestinal signals *per se* does not require gastric emptying to be slowed.

Glucagon-like peptide-1

Much research effort has been focussed on intestinal L-cells due to their ability to broadly detect digestion products of carbohydrates, fats and proteins, and in response, secrete the incretin hormone GLP-1. L-cells are distributed throughout the GI tract, with greatest density in the distal intestine (ileum, colon); yet not insignificant numbers are present in the proximal small intestine in most species (Bryant *et al.*, 1983; Eissele *et al.*, 1992). These cells use alternative post-translational processing of proglucagon to produce the bioactive peptides GLP-1, GLP-2 and oxyntomodulin, although most attention has focussed on the actions of GLP-1 (Holst, 2007). GLP-1 is released rapidly in proportion to caloric load and to the length of small intestine exposed to nutrient, and acts to increase satiation, stimulate insulin release, suppress glucagon secretion and slow gastric emptying (Schirra and Goke, 2005; Horowitz and Nauck, 2006; Little *et al.*, 2006). In addition, complex carbohydrates that reach the distal intestine may be fermented to short-chain fatty acids, which can also interact with L-cells via other nutrient sensors (Holst, 2007; Reimann, 2010). While these distal L-cell mechanisms can powerfully influence GI motility and food intake (as the ileal and colonic brake mechanisms), they may not be signifi-

cantly recruited under normal GI transit due to effective upper gut absorption; they are also less likely to signal via a vagal pathway.

Our own work has shown that a subset of proximal intestine L-cells in both mice and humans express GPCRs for sweet taste (Sutherland *et al.*, 2007; Young *et al.*, 2010). Sweet taste receptors are under dynamic luminal and metabolic control, and link the luminal presence of a broad range of sweet tastants, including sweeteners, to the intestinal release of GLP-1 (for review, see Young, 2011). In L-cell-based systems, and recently in human intestine, it has been shown that blockade of sweet taste receptors reduces glucose-stimulated GLP-1 [and peptide YY (PYY)] release, while mice that are deficient in sweet taste molecule expression show dysregulated glucose-stimulated GLP-1 release (Jang *et al.*, 2007; Margolskee *et al.*, 2007; Gerspach *et al.*, 2011). Sweet taste receptors provide one example, among others, of sensors expressed on L-cells, which may transduce luminal carbohydrate signals (Tolhurst *et al.*, 2009). A similarly diverse list of candidate GPCRs in the intestine respond to breakdown products of amino and fatty acids leading to the release of GLP; these have been reviewed by others [see Table 1 (Little and Feinle-Bisset, 2011b; Reimann, 2010)].

The functional importance of GLP-1 in food intake control is now well established – genetic variation around the GLP-1 allele strongly correlates with total food volume in mice strains (Kumar *et al.*, 2008), while mice deficient in GLP-1 receptors are partially resistant to HFD-induced obesity (Hansotia *et al.*, 2007). Evidence indicates that effects of gut-released GLP-1 on food intake are mediated largely via a vagal pathway arising from the proximal intestine (Hayes *et al.*, 2011). Subdiaphragmatic vagotomy completely blocks the satiating effect of intraperitoneal GLP-1 infusion (targeting intestinal vagal afferents) in rats, indicating that these effects are dependent on vagal afferent activation (Punjabi *et al.*, 2011). Indeed, GLP-1 receptors have been localized on abdominal vagal afferents, on nodose ganglion neurons and in brainstem neurons (notably within the dorsal vagal complex) (Drucker and Asa, 1988; Goke *et al.*, 1995; Imeryuz *et al.*, 1997; Merchenthaler *et al.*, 1999; Kakei *et al.*, 2002; Nakagawa *et al.*, 2004). While GLP-1 has also been shown to excite vagal afferents directly, effects on satiety and gastric emptying were long considered to involve endocrine actions at central sites within brainstem and hypothalamic nuclei (Imeryuz *et al.*, 1997; Kakei *et al.*, 2002; Nagell *et al.*, 2006; Nakade *et al.*, 2006; Bucinskaite *et al.*, 2009; Holmes *et al.*, 2009). However, the relative importance of central site of action for gut-released GLP-1 is uncertain as GLP-1 undergoes rapid degradation within minutes at the site of peripheral release and within the circulation and liver by the ubiquitous enzyme dipeptidyl peptidase-IV (DPP-IV), with less than 10% reaching systemic circulation in intact form (Deacon *et al.*, 1996; Holst, 2007). Moreover, circulating levels of active GLP-1 do not significantly rise after regular chow meals in non-anaesthetized rats (Punjabi *et al.*, 2011), suggesting that the normal signalling mode of gut-derived GLP-1 is predominantly paracrine (vagal), rather than endocrine. It should be noted, however, that GLP-1 is also produced centrally within autonomic neurons of the ventrolateral and caudal nuclei of the solitary tract, which project to various hypothalamic nuclei, and direct activation of GLP-1 receptors within the caudal brainstem is capable of reducing food intake (Merchenthaler *et al.*, 1999; Vrang *et al.*, 2007; Hayes *et al.*, 2008; Llewellyn-Smith *et al.*, 2011). However, blockade of central GLP-1 receptors does not block the anorexia induced by intraperitoneal GLP-1 in rats, whereas peripheral GLP-1 receptor blockade led to increased light phase food intake in rats (Williams *et al.*, 2009), arguing against a prominent role of central GLP-1 in intestinal vagal afferent-mediated satiety. In summary, it appears that gut-derived GLP-1 is the primary satiety signal triggered upon food intake, and that vagal processing is sufficient to exert this effect.

It is also well established that the peripheral administration of GLP-1 or GLP-1 analogues (e.g. exenatide, liraglutide) dose dependently reduce food intake leading to weight loss in animal models of obesity and in lean and obese humans (for review, see Hayes *et al.*, 2010). In rats, this reduced food intake with liraglutide is due to combined actions at GLP-1 receptors on peripheral vagal afferents of the intestine (or hepatic portal region) and centrally (Kanoski *et al.*, 2011). Peripheral GLP-1 also directs energy balance on both a short- and long-term basis via interaction with leptin, which is hypothesized to increase intestinal vagal afferent sensitivity to GLP-1, as occurs for another anorexigenic peptide, CCK. Thus, a satiating effect of GLP-1 in fasted mice is revealed by co-administration with leptin, and GLP-1 is ineffective in reducing food intake in leptin receptor-deficient mice. Both CNS and peripheral sites of action appear plausible for this action (for review, see Barrera *et al.*, 2011).

Glucose-dependent insulinotropic peptide (GIP)

GIP-secreting K-cells are located within the proximal small intestine, and are responsive to digestion products of carbohydrates and fat, as well as certain amino acids (Baggio and Drucker, 2007). GIP is rapidly released postprandially in proportion to calorific load (Pilichiewicz *et al.*, 2007a), and acts to stimulate insulin release and promote lipid storage in adipocytes, the latter an emerging role that may link overnutrition to obesity (Yip *et al.*, 1998; Baggio and Drucker, 2007; Kim *et al.*, 2007). There is recent interest in GIP in the obesity setting, given that GIP knockout mice are resistant to diet-induced obesity (Miyawaki *et al.*, 2002). Indeed, it has been proposed that part of the benefits of Roux-en-Y gastric bypass in obesity management may be due to surgical removal of intestinal K-cells (for review, see Paschetta *et al.*, 2011). However, in contrast to GLP-1, exogenous GIP does not alter the rate of gastric emptying in response to intestinal carbohydrates, and correspondingly, vagal afferents in rodents lack receptors and functional responses to GIP (Nishizawa *et al.*, 1996; Meier *et al.*, 2004; Nakagawa *et al.*, 2004). Moreover, while the density of intestinal K-cells may increase in obesity, GIP has no direct effects on hunger, desire to eat, satiety or prospective consumption in humans (Cho and Kieffer, 2011; Edholm *et al.*, 2011). It should be noted that K-cells co-secrete the peptide xenin, which exerts satiating effects at a peripheral and/or central site of action, the latter which may occur independent of known hypothalamic satiety centres (Leckstrom *et al.*, 2009; Taylor *et al.*, 2011). It remains to be established whether a peripheral vagal pathway is involved in this action of xenin.

Peptide YY

PYY is produced within L-cells that co-secrete GLP-1 in both the proximal and distal intestine, and is released in response to fatty acids, carbohydrates and to a lesser extent, amino acids (for review, see Holst, 2007). PYY release is in proportion to caloric load and acts to both increase satiation and slow gastric emptying (Batterham *et al.*, 2006; Pilichiewicz *et al.*, 2007b; Helou *et al.*, 2008). Two endogenous forms mediate these effects, with $PYY_{3–36}$ – the predominant circulating form – produced following cleavage of $PYY_{1–36}$ in circulation by the ubiquitous enzyme DPP-IV (Karra *et al.*, 2009). Along with other members of this peptide family (neuropeptide Y, pancreatic polypeptide), PYY peptides interact with specific GPCRs Y1, 2, 4, 5 and 6 with differential specificity; $PYY_{1–36}$ binds to all Y-class receptors, while $PYY_{3–36}$ shows high affinity for Y2 receptors, and lower affinity for Y1 and Y5 receptors. Intraperitoneal administration of $PYY_{3–36}$ in rodents was shown to exert a dose-dependent anorectic effect on food intake (Batterham *et al.*, 2002), which could be completely blocked by subdiaphragmatic vagotomy (Abbott *et al.*, 2005). Indeed, Y2 receptors have been identified on both intestinal vagal afferents and within the hypothalamus (arcuate nucleus) indicating that anorectic effects of Y2 receptor activation may be achieved via paracrine activation of intestinal vagal afferents, via direct central activation by circulating $PYY_{3–36}$, or by both pathways (Zhang *et al.*, 1997; Fetissov *et al.*, 2004; Koda *et al.*, 2005). Like GLP-1, PYY has complex effects on food intake upon central administration in rodents. Direct administration to the hypothalamic arcuate nucleus inhibits food intake via a Y2 receptor-dependent manner, while i.c.v. administration exerts orexigenic effects in the hypothalamic paraventricular nucleus via a Y1 and Y5 receptor-dependent manner (for review, see Cummings and Overduin, 2007). Together, these findings highlight the complex role of Y2 receptors in both vagal and central pathways regulating satiety.

Vagal expression of Y2 receptors is known to be modified by feeding status in rats, and in association with prevailing levels of the gut hormone CCK. Thus, Y2 receptor levels are low in fasted mice and high in fed mice, or in fasted mice infused with CCK (Burdyga *et al.*, 2008). This action of CCK is mediated via release of the vagal afferent neuronal peptide derived from cocaine- and amphetamine-regulated transcript (CART), which acts in an autocrine manner to increase Y2 receptor levels (De Lartigue *et al.*, 2011; reviewed in Dockray and Burdyga, 2011). Pharmacological blockade of Y2 receptors in rats has been shown to abolish feeding inhibition by $PYY_{3–36}$, while germline knockout mice deficient in Y2 receptors are hyperphagic and develop obesity (Batterham *et al.*, 2002; Scott *et al.*, 2005); similar findings have been revealed in a PYY-specific knockout mouse (Naveilhan *et al.*, 1999). Thus, there is ample evidence to suggest that vagal Y2 receptors are an important satiety-signalling mechanism.

Cholecystokinin

CCK-secreting I-cells are located largely within the proximal small intestine and are more responsive to digestion products of fatty and amino acids than to carbohydrates (Rehfeld, 1978; Cummings and Overduin, 2007). It is well established that CCK release occurs in proportion to caloric load, but independent of the length of small intestine exposed (Liddle *et al.*, 1985; Little *et al.*, 2006). Release of CCK by fatty acids is critically dependent on acyl chain length, with only fatty acids ≥12 carbon atoms able to trigger release, and subsequent suppression of food intake (Hunt and Knox, 1968; McLaughlin *et al.*, 1999; Feltrin *et al.*, 2004). Short-chain fatty acids, in contrast, engage specific nutrient detectors in the distal intestine, which may influence satiety via non-vagal pathways as part of the ileal or colonic brake mechanisms (for review, see Kaemmerer *et al.*, 2010). Activation of intestinal vagal afferents by fat involves the packaging of fatty acids within enterocytes into chylomicrons, followed by the production and basolateral release of apolipoprotein A-IV; apolipoprotein A-IV then triggers CCK release, activating CCK_1 receptors on adjacent vagal afferent endings (Glatzle *et al.*, 2003; Whited *et al.*, 2006; Lo *et al.*, 2007). An alternate signal pathway for CCK-dependent activation of vagal afferents has also been proposed for oleoylethanolamine, a lipid amide that also triggers intestinal release of apolipoprotein A-IV in a manner dependent on the activation of peroxisome proliferator-activated receptor alpha (Fu *et al.*, 2003). However, much less is known of how CCK is released by proteins to activate intestinal vagal afferents. Evidence so far has revealed that the proton-coupled oligopeptide transporter PepT1 (peptide transporter 1) is indirectly involved via a CCK-dependent pathway (Darcel *et al.*, 2005; Matsumura *et al.*, 2005; Liou *et al.*, 2011).

There is abundant evidence from our laboratory, and others, that intestinal vagal afferents express the CCK_1 receptor, and are responsive to CCK (Cottrell and Iggo, 1984a; Moran *et al.*, 1987; Blackshaw and Grundy, 1990; Broberger *et al.*, 2001; Lal *et al.*, 2001; Partosoedarso *et al.*, 2001). Exogenous administration of CCK potently suppresses food intake and slows gastric emptying in rats and humans – effects blocked by vagotomy in rats (Smith *et al.*, 1985; Schwartz *et al.*, 1993; Sullivan *et al.*, 2007; Brennan *et al.*, 2008). In a similar manner, pharmacological blockade of CCK_1 receptors dose dependently inhibits food intake and gastric emptying effects of exogenous and endogenous CCK in rats and humans (Fried *et al.*, 1991; Moran *et al.*, 1992; 1994; Yox *et al.*, 1992; Beglinger *et al.*, 2001). Genetic polymorphisms around the CCK (and leptin) allele in humans have also been shown to associate with specific eating patterns and meal size (de Krom *et al.*, 2007), supporting a specific role for CCK in human satiety signalling. Despite strong evidence of a peripheral site of action, a central site for CCK satiety has been shown, based on expression and function of CCK receptors in hypothalamic satiety centres, and evidence that blood–brain barrier permeant CCK_1 receptor antagonists modify food intake in vagotomized rats (Schick *et al.*, 1990; Honda *et al.*, 1993; Reidelberger *et al.*, 2004). A recent and elegant magnetic resonance study in humans, however, has revealed that activation of brain regions upon intestinal exposure to intralipid was consistent with activation via a vagal pathway, and could be abolished by pharmacological blockade of CCK_1 receptors (Lassman *et al.*, 2010). Satiation in humans in response to long-chain fatty acids, and gastric emptying of hexose sugars are also reported to be blocked by the CCK_1 receptor antagonist loxiglumide (Matzinger *et al.*, 2000; Little *et al.*, 2010), highlighting the importance of CCK satiety signals in response to a range of dietary macronutrients. Levels of CCK_1 receptors in vagal afferents do not show

significant nutritional plasticity in health, but serve as triggers to modulate levels of other anorexic and orexigenic receptors with feed status (for review, see (Dockray and Burdyga, 2011). CCK activation of vagal afferents and satiety signalling, though, is inhibited by orexigenic hormones including ghrelin, orexin A and the endogenous cannabinoid receptor agonist, anandamide (Burdyga *et al.*, 2006a; 2010; 2006b; De Lartigue *et al.*, 2011). In contrast, CCK activation of a subset of CCK_1 receptor expressing vagal afferents is likely to be potentiated by anorectic actions of melaninocortin-4 receptor agonists (such as α-melanocyte-stimulating hormone) acting via a central presynaptic mechanism (Wan *et al.*, 2008; Gautron *et al.*, 2010), as well as by leptin.

CCK acts predominantly as a short-term satiety signal, as long-term administration in animals and humans does not alter body weight, as reduced meal size is effectively offset by increased meal frequency. In fact, the satiating actions of intraperitoneal CCK administration are lost as early as 24 h in rodents (Crawley and Beinfeld, 1983; West *et al.*, 1984). However, anorectic effects of CCK are augmented by the long-term satiety hormone leptin, when CCK responses are potentiated at the level of vagal afferents, the brainstem and hypothalamus (for review, see Strader and Woods, 2005; Dockray and Burdyga, 2011). Accordingly, the adiposity of an individual, which is tightly linked to circulating leptin levels, is likely to sculpt responsiveness to short-term CCK signals. For example, anorectic effects of CCK would likely be decreased in both lean individuals and in leptin-resistant states, such as obesity. It is also important to note that rats deficient in CCK_1 receptor expression are obese and hyperphagic, while mice lacking CCK_1 receptors are lean, but become obese following a HFD (Schwartz *et al.*, 1999; Bi *et al.*, 2007); variable effects of a HFD have been reported in CCK knockout mice (Lacourse *et al.*, 1999; Lo *et al.*, 2011). Together, these data indicate that CCK exerts acute anorectic effects on meal size and timing, but exerts these actions predominantly via peripheral vagal actions to control food intake.

Serotonin (5-HT)

Serotonin-secreting enterochromaffin (EC) cells are a prominent enteroendocrine cell type distributed throughout the GI tract. EC cells release 5-HT in response to a wide array of chemical and mechanical cues, including acids, bases, carbohydrates, long- and short-chain fatty acids, as well as following distension or exposure to high-osmolarity stimuli (for reviews, see Grundy, 2006; 2008; Blackshaw *et al.*, 2007; Bertrand, 2009; Raybould, 2009; Bertrand and Bertrand, 2010). Vagal afferents in rats and humans are known to express the $5\text{-}HT_3$ receptor, while in rats, both $5\text{-}HT_{3A}$ and $5\text{-}HT_{3B}$ subtypes are expressed and may form homomeric or heteromeric receptors each with different agonist sensitivity (Glatzle *et al.*, 2002; Morales and Wang, 2002; Lang and Grafe, 2007). Following GI release, 5-HT exerts paracrine effects via activation of 5-HT receptors present on enteric nerves and vagal nerve endings within the mucosa; circulating 5-HT levels are kept low due to specific uptake into platelets. A number of other bioactive compounds have been identified in EC cell populations, including chromogranin A, melatonin, ATP, GABA, uroguanylin and dynorphin although less is known of their actions in the GI tract (see Bertrand and Bertrand, 2010).

While parenteral 5-HT administration has been shown to reduce meal size and duration in rats, vagotomy appears to increase this effect (Fletcher and Burton, 1985; 1986). Additionally, outcomes of studies using $5\text{-}HT_3$ receptor antagonists to influence satiety in animals and humans have generally been inconsistent, raising questions for a peripheral role of 5-HT in food intake regulation (for review, see Aja, 2006). Indeed, most attention has been focussed on central sites of satiety actions of 5-HT acting on $5\text{-}HT_1$ and $5\text{-}HT_2$ receptor subtypes (for review, see Atkinson, 2008). Despite this, evidence in rodents has indicated a role of peripheral $5\text{-}HT_3$ receptors in vagal pathways activated by carbohydrate, fatty acids and hyperosmolar stimuli leading to suppression of food intake, slowing of gastric emptying and pancreatic secretion (Li *et al.*, 2000; Zhu *et al.*, 2001; Raybould *et al.*, 2003; Savastano *et al.*, 2005; 2007; Wu *et al.*, 2005). It has also been suggested that similar populations of intestinal vagal afferents activated by CCK in rats are responsive to 5-HT (Li *et al.*, 2004); this could potentiate satiety signal arising in this common pool of vagal afferents, particularly in the presence of mixed meal components. A similar mechanism has been shown for gastric vagal afferent mechanosensitivity, which is augmented by both CCK and 5-HT and has been suggested is the primary peripheral satiety action of peripheral 5-HT (Bozkurt *et al.*, 1999; Daughters *et al.*, 2001; Hayes *et al.*, 2006). Additional experiments are required to ascertain the precise role of peripheral GI release of 5-HT and vagal $5\text{-}HT_3$ receptors in food intake regulation, although this contribution is likely to be less than other direct vagal mediators of satiety.

Intestinal vagal afferent signals in obesity

Studies in rodents following a HFD, or in diet-induced obesity consistently show reduced suppressive effects of intestinal nutrients on food intake compared to control animals (Covasa *et al.*, 2001; Little and Feinle-Bisset, 2011b). Moreover, the GI release of GLP-1 and PYY is reported to be attenuated in diet-induced obesity in rodents, while CCK and 5-HT release is increased (Spannagel *et al.*, 1996; Anini and Brubaker, 2003; Batterham *et al.*, 2006; Bertrand *et al.*, 2011). Satiety effects of exogenous (intraperitoneal) CCK, however, are attenuated in rodents fed with a HFD (Covasa and Ritter, 1998; Nefti *et al.*, 2009) as are nodose ganglion levels of CCK_1 receptor expression, changes that mirror those reported in vagal afferents following injury or nerve damage (Zhang *et al.*, 1996; Broberger *et al.*, 2001). In contrast, anorectic effects of exogenous PYY and GLP-1 appear to be preserved in rodent models of diet-induced or genetic obesity (Neary *et al.*, 2005; Renshaw and Batterham, 2005; Vrang *et al.*, 2006; Madsen *et al.*, 2011; Tomas *et al.*, 2011). A recent study in mice directly tested intestinal afferent function in diet-induced obesity and showed reduced sensitivity of jejunal afferents (primarily vagal) to low-level distension and reduced excitability of identified jejunal vagal afferents within the nodose ganglion to CCK and 5-HT exposure (Daly *et al.*, 2011). Corresponding reductions in vagal afferent expression of receptors for CCK, 5-HT and other anorexic GI

peptides have been reported in the nodose ganglion of mice subjected to short- and long-term HFDs, along with reduced brainstem expression of c-fos following a meal stimulus (Donovan *et al.*, 2009; Nefti *et al.*, 2009).

In humans, reports indicate that both fasting and post-prandial levels of circulating PYY and GLP-1 are also lower in obese, compared to lean individuals (Batterham *et al.*, 2003; le Roux *et al.*, 2006; Little and Feinle-Bisset, 2011a). CCK levels, in contrast, are either increased (Baranowska *et al.*, 2000) or normal in obese individuals (Lieverse *et al.*, 1994). There are, however, a number of caveats in comparing many of these human studies. One example is that the reduced slowing of gastric emptying that occurs on a HFD (Cunningham *et al.*, 1991) would itself act to increase intestinal exposure and increase GI peptide release. Despite this generalized attenuation in GI peptide release, the anorectic effects of exogenously administered CCK, PYY and GLP-1 appear to be preserved in obese individuals (Flint *et al.*, 2001; Batterham *et al.*, 2003). In summary, it appears that attenuated GI peptide release and lower sensitivity of intestinal vagal pathways can both contribute to reduced signalling of satiety and reduced suppression of food intake in obesity.

Conclusions

Together, these data indicate that sensing of mechanical and nutrient cues within the wall of the GI tract, and signalling of satiety by vagal pathways, represent a major regulatory interface in the control of food intake and satiation. As such, therapies that target such vagal mechanisms are likely to yield effective new management strategies, and a viable target to curb obesity and metabolic disease. Although a number of mechanisms have already been implicated in these actions, their precise mechanisms in the gut and mode of vagal signalling of satiety remain to be fully revealed. This is a promising new arena for clinical and translational research in obesity management.

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Conflict of interest

None of the authors have any conflict of interest, financial, academic or otherwise.

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