Proceedings of the Nutrition Society (2012), **71**, 446–455 doi:10.1017/S0029665112000110
 First published online 27 March 2012

The Winter meeting of the Nutrition Society was held at the Royal College of Physicians, London on 6–7 December 2011

70th Anniversary: Body weight regulation – food, gut and brain signalling Symposium I: Food–gut interactions

Nutrient sensing and signalling by the gut

Rojo Rasoamanana[1,2], Nicolas Darcel[1], Gilles Fromentin[2] and Daniel Tomé[1]*
[1]*AgroParisTech, CRNH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, F-75005 Paris, France*
[2]*INRA, CRNH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, F-75005 Paris, France*

Recent advances highlight that nutrient receptors (such as T1R1/T1R3 heterodimer, Ca sensing receptor and GPR93 for amino acids and protein, GPR40, GPR41, GPR43 and GPR120 for fatty acids, T1R2/T1R3 heterodimer for monosaccharides) are expressed in the apical face of the gut and sense nutrients in the lumen. They transduce signals for the regulation of nutrient transporter expressions in the apical face. Interestingly, they are also localised in enteroendocrine cells (EEC) and mainly exert a direct control on the secretion in the lamina propria of gastro-intestinal peptides such as cholecystokinin, glucagon-like peptide-1 and peptide YY in response to energy nutrient transit and absorption in the gut. This informs central nuclei involved in the control of feeding such as the hypothalamus and nucleus of the solitary tract of the availability of these nutrients and thus triggers adaptive responses to maintain energy homoeostasis. These nutrient receptors then have a prominent position since they manage nutrient absorption and are principally the generator of the first signal of satiation mechanisms mainly transmitted to the brain by vagal afferents. Moreover, tastants are also able to elicit gut peptides secretion via chemosensory receptors expressed in EEC. Targeting these nutrient and tastant receptors in EEC may thus be helpful to promote satiation and so to fight overfeeding and its consequences.

Nutrient sensing: Gut–brain interaction: Signalling pathway

Studies conducted over the last few decades have greatly improved the understanding of the mechanisms by which the gut senses luminal nutrients and the role of the gut–brain axis in the homeostatic control of energy metabolism in response to fasting or feeding (Fig. 1 and Table 1). On the basis of very recent advances it has been shown that intestinal luminal nutrients (such as carbohydrate, fat and protein) are sensed by specific 'taste' receptors or transporters located in the membrane of cells in the intestinal epithelium[(1–3)]. This sensing of nutrients by enteroendocrine cells (EEC) located in the intestinal epithelium triggers the release of gastro-intestinal (GI) regulatory peptides such as ghrelin, serotonin (5-hydroxytryptamine), cholecystokinin (CCK), peptide tyrosine–tyrosine (PYY) and/or glucagon-like peptide-1 (GLP-1) as important players involved in the gut–brain connection[(4–8)]. These GI peptides can exert their regulatory effects in a paracrine way by acting locally on specific receptors of vagal afferent nerves termination that project in the nucleus of the tractus solitary at the level of the brainstem. They can also exert their regulatory effects in an endocrine fashion after entering the systemic circulation or the lymphatic system and acting on receptors located in the arcuate nucleus at the level of the hypothalamus or in the area postrema at the level of the brainstem, two areas sensitive to blood-borne signals, respectively. Because of rapid break down by proteases, the most important concentration of GI peptides is found near the site of secretion in the lamina propria, and the paracrine action via the vagus nerve is probably a more potent signal transmitter to the brain[(9)]. The afferent vagal is made up of extrinsic primary afferent neurons with cell bodies located in nodose ganglia and projecting to the brainstem, of intraganglionic laminar endings located between the circular and longitudinal muscle layers of the

Abbreviations: CaR, Ca sensing receptor; CCK, cholecystokinin; EEC, enteroendocrine cells; GI, gastro-intestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; LCFA, long-chain fatty acid; PLCβ2, phospholipase Cβ2; PYY, peptide tyrosine–tyrosine; S-GLT1, Na–glucose ATP co-transporter.

***Corresponding author:** Professor Daniel Tomé, fax +33 144087248, email tome@agroparistech.fr

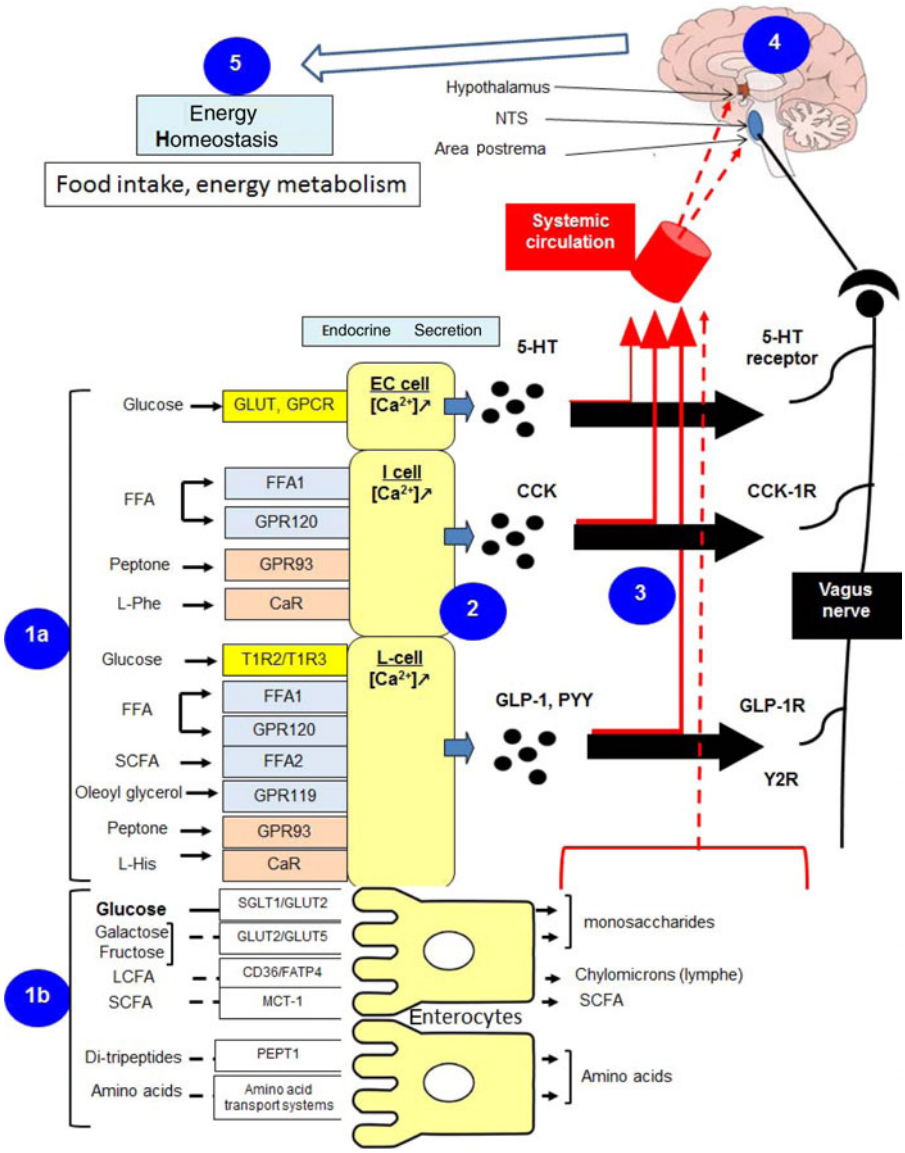

Fig. 1 (colour online) Consequences of nutrient sensing on the gut-to-brain signalling involved in the control of food intake. (1a) Nutrients are detected in the gut by their receptors expressed in the apical face of enteroendocrine cells. (1b) This sensing stimulates nutrient absorption through nutrient carriers in the brush border membrane of epithelial cells (as precisely described for glucose). (2) Inward Ca concentration of enteroendocrine cells increases consequently to the detection of nutrient. This leads to the release of gastro-intestinal peptides such as serotonin (5-HT), cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide tyrosine–tyrosine (PYY), in the lamina propria. In a paracrine pathway via their receptors expressed in the ending nerves of enteric nervous system, these gastro-intestinal peptides transmitted signal of nutrient availability to the brain by vagus nerve mainly. Systemic circulation is secondarily used in this signalling. (4) Nucleus of the tractus solitary receives and integrates signalling from vagus nerve while systemic signalling reaches in the arcuate nucleus of hypothalamus and area postrema in the brainstem. (5) Hypothalamo-brainstem integrating network of this signal allows homoeostatic control of feeding. EC-cell, endocrine cell; FFA, NEFA; GPR, G protein-coupled receptor; L-His, L-histidine; L-Phe, L-phenylalanine; CaR, Ca sensing receptor; MCT-1, monocarboxylate transporter isoform 1; NCS, nucleus of the solitary tract; Y2R, Y2 receptor.

oesophagus, stomach and small intestine, and of intramuscular arrays located in the oesophagus and stomach. These branches of the vagus nerve that convey information from the gut to the brain are sensitive to mechanosensory stimuli (generated by bolus transit stretch on gut mucosa)[10] and also express GI peptide receptors[11]. Accordingly, nutrient infusion (as for the case of protein or glutamate) in the duodenum and stomach raises vagus nerve activity[12]. Subdiaphragmatic or total abdominal vagotomy significantly reduce the anorectic potency of CCK, GLP-1 and

https://doi.org/10.1017/S0029665112000110 Published online by Cambridge University Press

Table 1 Nutrient sensing and transport in the gut and gastro-intestinal peptides secretion

Nutrient and tastant	Receptor/transporter involved in the sensing	Receptor-expressing enteroendocrine cell	GI peptides secreted	References
Bitter tastants	T2R	I-cells	CCK	Geraedts *et al.*[38,39]
		L-cells	GLP-1	
Monosaccharides	T1R2/T1R3	L-cells	GLP-1, PYY	Gerspach *et al.*[35]
Glucose, galactose	S-GLT1, GLUT2, GLUT5	–	Not reported	
Fructose	GLUT5	–	Not reported	
Amino acids	T1R1/T1R3	–	Not reported	
	CaR	I-cells	CCK	Leech *et al.*[62], Hira *et al.*[63], Nakajima *et al.*[64]
		L-cells	GLP-1	
	GPRC6A	–	Not reported	
Peptone	GPR93	I-cells	CCK	Choi *et al.*[1]Cordier-Bussat *et al.*[66]
		L-cells	GLP-1	
Di, tri-peptide	PEPT1	–	CCK	Darcel *et al.*[68], Liou *et al.*[85]
Medium and long-chain fatty acids	NEFA1 (or GPR40)	L-cells	GIP, GLP-1	Edfalk *et al.*[72], Liou *et al.*[69]
	GPR120	I-cells	CCK	Tanaka *et al.*[83], Hirasawa *et al.*[2]
		L-cells	GLP-1	
	FAT CD36, FATP4	–	Not reported	
SCFA	NEFA2R (or GPR43)	Enterochromaffin cells	5-HT	Karaki *et al.*[91], Tazoe *et al.*[92]
		L-cells	PYY	
	NEFA3R (or GPR41)	Enterochromaffin cells	5-HT	Karaki *et al.*[91] Tazoe *et al.*[92]
		L-cells	PYY	
SCFA	MCT-1	–	Not reported	

GI, gastro-intestinal; GIP, glucose-dependent insulinotropic polypeptides; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; GPR, G protein-coupled receptor; PYY, peptide tyrosine–tyrosine; CaR, Ca sensing receptor; PEPT1, peptide transporter 1; S-GLT1, sodium-dependent glucose transporter 1; 5-HT, 5-hydroxytryptamine; FAT, fatty acid transporter; FATP, fatty acid transport protein; MCT-1, monocarboxylate transporter isoform 1.

PYY[13–15] and tetracaine treatment (which desensitises vagus nerve fibres in the lamina propria) inhibits lipid-induced satiation and CCK-induced decrease in hepatic glucose production[16,17]. However, both the vagus-mediated pathways and a blood pathway are involved in the transfer of nutrient and GI peptide-associated information from the gut to the brain, and although the vagus nerve appears as the main pathway of gut–brain signalling compensatory mechanisms using systemic circulation and/or lymphatic transport appear when the vagus pathway is abolished[18].

Sensing monosaccharide and taste stimuli in the gut

Digestible carbohydrates commonly found in food are monosaccharides (such as glucose, galactose and fructose), disaccharides (such as sucrose and lactose) and complex carbohydrates coming from plant (starch) or animal products (glycogen). These are broken down to monosaccharides by digestive enzymes (such as α-amylase, β-amylase and β-glucosidase) before absorption. According to current studies, chemical signals are monosaccharides and tastants acting on taste receptors.

Chemosensory receptors for taste stimuli in the gut

Receptors of the G-protein-coupled T1R and T2R families sensitive to taste stimuli and monosaccharides have been identified in the mouth and the gut epithelium. Bitter taste involves T2R receptor family[19] whereas among the subtypes of the T1R family, the heterodimers T1R1/T1R3 and T1R2/T1R3 sense umami and sweet taste, respectively[3]. The α-subunit of the G proteins gustducin and transducin mediate the downstream signalling of sweet, bitter and umami tastes through T1R and T2R families[20,21]. Triggered by α-gustducin or α-transducin, the enzyme phospholipase Cβ2 (PLCβ2) catalyse the formation of inositol 4,4,5-triphosphate leading to an increase in intracellular Ca. This further activates Trpm5 (transient receptor potential channel 5), thus facilitating entry of monovalent cations for the taste signalling[22].

Taste stimuli are initially sensed in the epithelial cells of the lingual bud, but the expression of the taste receptors or their downstream enzymes has also been demonstrated in different parts of the gut. In mice, expression was shown of T1R1, T1R3, PLCβ2 and Trpm5 transcripts in the stomach and of T1R1, T1R2, T1R3, α-gustducin, PLCβ2 and Trpm5 in the intestine[23]. In addition, transcripts of T1R2 and T1R3 were observed in mice and rat intestine[24,25], of T1R3 in a human colon cell line[26] and of the T2R family in mice and human intestine[26,27]. Moreover, α-gustducin and α-transducin were found in rat and mouse epithelial gastric mucosa cells, in rat pancreatic endocrine cell line AR42J and in the duodenal mouse cell line STC-1, whereas PLCβ2 and Trpm5 were seen in mouse and rat intestinal cells[27,28].

Monosaccharide receptor and transport systems in the gut

Monosaccharides (such as glucose, galactose and fructose) having sweet taste are detected by the chemoreceptor T1R2/T1R3 heterodimer expressed in the gut. This receptor senses luminal glucose and monosaccharide

https://doi.org/10.1017/S0029665112000110 Published online by Cambridge University Press

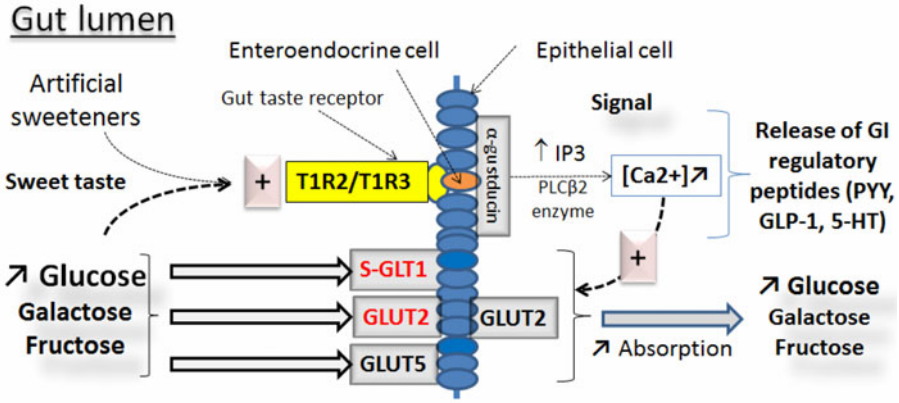

Fig. 2 (colour online) Sensing of nutrient by enteroendocrine cells potentiates nutrient absorption. The chemoreceptor T1R2/T1R3 senses luminal carbohydrate and transduces signal to α-gustducin triggering phospholipase Cβ2 (PLCβ2) enzyme that catalyses the formation of IP3 leading to an increase in intracellular (Ca^{2+}). Consequently, gastro-intestinal peptides such as glucagon-like peptide-1 and peptide tyrosine–tyrosine are released and carbohydrate transporters such as S-GLT1 and GLUT2 are up regulated or highly recruited at the enterocyte level to promote carbohydrate absorption. Sensing of artificial sweeteners by the same chemoreceptor may favour this phenomenon. PYY, peptide tyrosine–tyrosine; 5-HT, 5-hydroxytryptamine; GLP-1, glucagon-like peptide-1.

concentration and transduces an adaptive response to transporter expression or recruitment in the apical membrane of enterocytes in order to regulate monosaccharide absorption.

Apical absorption of monosaccharides through the duodenal brush border membrane requires the Na–glucose ATP co-transporter (S-GLT1) for glucose and galactose and the facilitating transporters GLUT2 and GLUT5 for fructose[29]. In the basolateral membrane of enterocytes, GLUT2 is a sensor of inward glucose, galactose and fructose with their external concentration[30]. With high luminal concentration of glucose, GLUT2 reached the apical brush border membrane of intestinal cells and expression of S-GLT1 was also up-regulated to potentiate glucose absorption, and this seemed to be under the control of chemoreceptors that sense glucose availability. In fact, levels of both the mRNA and protein of S-GLT1 were increased 2-fold in mice fed a 70% sucrose diet whereas in T1R3 $^{-/-}$ or α-gustducin $^{-/-}$ mice a high-sucrose diet was unable to up regulate S-GLT1[31]. Moreover, it was suggested that a constitutive S-GLT1 expression permits glucose absorption under normal concentration and inducible expression of S-GLT1 occurs in high luminal glucose level[32].

Furthermore, artificial sweeteners such as acesulfame K, sucralose and saccharin detected by the heterodimer chemoreceptor T1R2/T1R3 also promote glucose absorption and trafficking in the brush border at least through high recruitment of GLUT2. An increase in the chemoreceptor downstream PLCβ2 protein expression is observed concomitantly with a high recruitment of GLUT2 in the apical membrane of rat jejunum cells within 30 min of exposure to artificial sweetener and low-glucose concentration or high-glucose concentration alone[25]. As high postprandial glycaemia contributes to insulin resistance and GLUT2 remains highly expressed in the apical membrane during it[33], this raises the question of whether artificial sweeteners prevent or favour insulin resistance (Fig. 2).

Monosaccharide and sweeteners sensing and gut endocrine functions

Taste stimuli and monosaccharides can be sensed along the gut and induce the secretion of GI regulatory peptides by EEC. The transductor α-gustducin was revealed in EEC[26,34] and this downstream signalling, by inducing membrane depolarisation and increasing intracellular Ca, leads to the release of GI peptides.

According to current results, glucose potently elicits GI peptide secretion including 5-hydroxytryptamine, PYY and GLP-1 but not CCK[35]. Enterochromaffin cells that express transporters for monosaccharides (such as S-GLT1) and salts (such as the apical sodium-dependent bile salt transporter), and receptors for tastants (such as T2R) and olfactants (such as OR1G1), secrete the anorectic peptide 5-HT in response to glucose, artificial sweeteners, Na, tastants (such as caffeine and tyramine) and olfactants (such as eugenol and thymol), respectively[36]. In addition, the heterodimeric sweet taste receptor T1R2/T1R3 senses monosaccharide availability in the gut and this seems to be involved in GI peptide PYY and GLP-1 secretion. This role has been supported by different observations including the co-localisation of the downstream taste signalling protein α-gustducin with PYY and GLP-1 in intestinal human L-cell line NCI-H716[26], the marked decrease of GLP-1 secretion after glucose exposure by isolated L-cells from α-gustducin null mice[37], the suppression of glucose-induced GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) secretion in α-gustducin $^{-/-}$ and T1R3 $^{-/-}$ mice[11], and finally the impaired GLP-1 and PYY secretion in response to glucose after blockade of the heterodimer receptor T1R2/T1R3 by lactisole in human subjects[35].

https://doi.org/10.1017/S0029665112000110 Published online by Cambridge University Press

Bitter tastants, artificial sweeteners and other tastants are also able to induce GI peptide secretion. Similarly to the T1R receptors family, T2R receptors are thought to trigger α-gustducin and PLCβ2 signalling leading to intracellular influx of Ca^{2+}. In the STC-1 cell line (a model of EEC), it was shown that in response to bitter tastants such as denatonium benzoate and quinine, CCK and GLP-1 secretion is dose-dependent on Ca^{2+} influx, an effect also observed with Cl and acetic acid for sourness, NaCl for saltiness and the artificial sweetener sucralose[38,39]. In addition, non-digestible carbohydrates such as resistant starch, gums (e.g. guar gum), pectins or psyllium, which are also called dietary fibre are able to elicit gut peptide secretion[40] but their detection in the gut is less explored.

Sensing of protein, peptides and amino acids in the gut

In the GI lumen, proteins are broken down by digestive enzymes to small peptides and amino acids that are absorbed by specific transport systems in the intestinal epithelial cells. Amino acid and peptide signals are sensed in the gut and their downstream signalling also induces GI peptide secretion.

Amino acid and peptide-sensitive receptor systems

In the bud and intestinal lumen, glutamate in the monosodium form is acknowledged generating 'umami' taste through the T1R1/T1R3[41]. This heterodimer T1R1/T1R3 also senses L-amino acid availability in the gut. Amino acid sensing depends upon the enantiomer: the natural stereo-isoform L- can bind to the heterodimer taste receptor T1R1/T1R3 unlike D-amino acids that have a broadly sweet taste and are sensed by the heterodimer receptor T1R2/T1R3 (as are artificial sweeteners and monosaccharides)[42]. Notably, the truncated metabotropic glutamate receptor mGluR4 was previously thought to mediate umami taste[43]. Besides, neurotransmission of glutamate is active inside the gut because nerve endings are thought to be missing in the luminal membrane. Visceral glutamate neurotransmission via mGluR5 receptor has recently been focused on because its inhibition may reduce visceral pain and gastro-oesophageal reflux[44].

Beyond this, other specialised receptors for amino acids include the Ca sensing receptor (CaR) that detects mainly aromatic L-amino acids (such as L-phenylalanine and L-tryptophan) and in a moderate fashion some aliphatic and polar L-amino ones (such as L-alanine)[45,46]. Amino acids and Ca, the main ligands of CaR, have two different binding sites. The G-protein-coupled receptor CaR becomes an aromatic L-amino acid receptor under stable and up to a threshold concentration of Ca^{2+} (1 mM)[47]. Immunohistochemistry demonstrated a broader expression of CaR on epithelial cells and neurons of the stomach, large and small intestine. Interestingly, detection of amino acids by CaR in the stomach leads to a secretion of gastric acid, pepsinogen and mucus[47,48]. In addition, the G-protein-coupled receptor GPRC6A that senses basic amino acids (such as L-lysine and L-arginine) and is expressed in the gastric mucosa and pancreas but not the small intestine[49] could also induce gastric acid and pepsinogen secretion as CaR. Moreover, GPRC6A activity seems to be dependent on Ca^{2+} and it shares the same site of Ca binding with CaR[50]. It then appears that CaR and GPRC6A are very similar except for the nature of amino acid they can sense. Lastly, it has been shown that peptone in the intestinal lumen is sensed by GPR93, a G-protein-coupled receptor of the A family that is highly expressed in the small intestine[1].

Amino acid transport and signalling in the cytosol

Amino acids and di- and tri-peptides are absorbed by specific transport systems in the gut. Usually, enterocytes and all mammalian cells try to maintain the intracellular concentration of amino acids to be equal to or greater than the extracellular pool. The presence of a multitude of amino acid transporters that can actively concentrate amino acids inside cells or support amino acids efflux facilitates this process.

Amino acid transport systems are present in membrane cells[51] including the apical membrane of the small intestine cells. Non-polar (alanine, glycine, isoleucine, phenylalanine, proline and tryptophan) and aliphatic (methionine, leucine and valine) amino acids cross the brush border membrane through System 1 (also called the B^0 system or SLC6A19 and B^0AT1 for the cDNA), which is a Na-dependent transporter. Cationic amino acids (arginine, lysine, ornithine and cystine) are transported by the antiport Na-dependent System 2 or $b^{0,+}$ system (SLC3A1 and SLC7A9), which exchange cationic with neutral amino acid. Imino acids transporter or System 3 (SLC6A20) works dependently on Na^+ and Cl^- to carry proline, hydroxy-proline and other *N*-methylated amino acids and analogues. Anionic amino acids (aspartic acid and glutamic acid) are absorbed via a proton, Na- and K-dependent transporter which is the System 5 or X^-_{AG} system (SLC1A1)[52]. Absorption of di- and tri-peptides, in enterocytes passes through proton-coupled oligopeptide transporters such as peptide transporter 1 (SLC15A1 gene) and peptide histidine transporter 1 (SLC15A4 gene) expressed in the duodenum and ileum of human subjects and rats[53,54]. Although it is important in peptide transport, peptide transporter 2 (SLC15A2 gene) is essentially expressed in the apical membrane of kidney, lung or spleen but not in the small intestine[55]. Of these peptide transporter 1 is the most relevant in intestine because its local disruption markedly decreases intestinal dipeptide absorption in mice[56].

Cellular amino acid sufficiency is controlled by GCN2 (general control non-repressed 2) which is activated in response to amino acid deficiency. It blocks protein synthesis except for a subset of proteins implicated in amino acid uptake such as activating transcription factor 4[57] and by mTOR (mammalian target of rapamycin) which is activated by an increase in amino acids and promotes both translation of gene involved in cell growth and inhibits GCN2 and AMP-activated protein kinase signalling associated with energy deficiency. In response to high-protein diet (which increases intracellular amino acid concentration), mammalian target of rapamycin was up regulated and AMP-activated protein kinase and GCN2 were reduced in liver[58] and possibly in gut cells.

NS Proceedings of the Nutrition Society

https://doi.org/10.1017/S0029665112000110 Published online by Cambridge University Press

Accumulation of branched chain amino acids (such as L-leucine) through System L is the most powerful stimulator of the mammalian target of rapamycin pathway[59].

Protein, peptide and amino acid sensing and gut endocrine function

Protein is a potent satietogenic nutrient[60,61] and this may be due to the ability of protein or its digestion products (peptides and amino acids) to induce pre- and post-absorptive signalling. Detection of both free amino acid and peptide transport influence GI secretion of CCK, PYY and GLP-1. In STC-1 cells, free amino acid sensing by CaR led to CCK and GLP-1 secretion[62,63]. Additionally, blocking CaR by NPS2143 abolished mobilisation of intracellular Ca^{2+} and CCK secretion[64]. Protein hydrolysates seem to be more potent at stimulating enteroendocrine function than free amino acids: in an earlier study, peptone treatment induced the secretion of CCK in isolated jejuno-ileal cells[65]. In STC-1 cells, peptone has been demonstrated to elicit the release of GLP-1[66] and CCK dependently on GPR93 protein receptor activation[67]. In addition, the peptide transporter 1 also appeared to be involved although indirectly in CCK secretion[68,69] by inducing membrane depolarisation and an increase in intracellular Ca^{2+}[70].

Sensing of fatty acids in the gut

During GI transit, under pancreatic TAG lipase and colipase action, food TAG are cleaved and release NEFA and monoacylglycerol the form of lipid being absorbed in the intestine[71]. Non-digestible carbohydrates, after being metabolised by gut microbiota (mainly phylum of Bacteriodetes and Firmicutes) in the distal intestine, generate SCFA whose receptors are broadly expressed in gut.

Fat-sensitive receptor and transporter systems

NEFA in lumen are sensed by a broad range of G-protein-coupled receptor depending on the length of their aliphatic chain. NEFA1 receptor (previously named GPR40) and GPR120 are responsive to medium- and long-chain NEFA (C>12)[2,72]. GPR120 is abundantly expressed in human and mouse intestine. SCFA such as acetate or butyrate from food or produced from gut fermentable dietary fibres in the distal intestine by gut microbiota, are detected by NEFA2 and NEFA3 receptors (previously termed as GPR43 and GPR41, respectively)[73,74]. Moreover, oleoylethanolamide, produced in the small intestine with fatty acid, is a ligand of GPR119[75].

Absorption of NEFA by enterocytes involves two carrier systems including fatty acid transporter CD36 (FAT CD36) and FATP (fatty acid transport protein 4). These transporters seem to be devoted to long-chain fatty acid (LCFA) translocation[76,77]. Although the efficient action of fatty acid transporter CD36 in LCFA absorption in intestine cells is acknowledged[77,78], the position of fatty acid transport protein 4 is unclear. In fact, in a study with a local deletion of FATP gene expression in mouse intestine, kinetics of fatty acid absorption, concentration of TAG in faeces, luminal concentration of fatty acid and feeding under a high-fat diet were not different between wild-type and transgenic mice, and a compensatory up regulation of other fatty acid carriers was missing (fatty acid transporter CD36)[79]. This implies that FATP is not crucial for fatty acid trafficking in the intestine. Another possible pathway of NEFA uptake is diffusion[80]. Transporters involved in the colonic transport of SCFA produced mainly from colon anaerobic fermentation of dietary fibre by microbiota are not clearly identified. Tissue culture studies (culture of human or rat colonocyte, Caco-2 cell line) have shown an apical active transport with HCO_3 exchange and an implication of monocarboxylate transporter isoform 1 in the colonic absorption of SCFA[81].

Fatty acid sensing and gut enteroendocrine cells functions

Unlike protein, it has been suggested that only detection of NEFA (the form being absorbed in gut) has an influence on GI peptide release. For instance, NEFA but not TAG were able to induce PYY and pancreatic polypeptide secretion in human subjects[82]. Elsewhere, perturbing the expression of GPR120 receptor in STC-1 cells impaired fatty acid-induced secretion of CCK and membrane depolarisation[83]. It appeared thus that CCK secretion depends upon GPR120 sensing. A recent study reported that Trpm5 requires intracellular Ca increase for its activation. Trpm5 is also involved in the CCK release induced by the sensing of lipid through GPR120[84]. Moreover, GLP-1 secretion in response to fat stimulation is dependent on GPR120[2]. Elsewhere, NEFA1 receptor, being expressed in I-cells, is implicated in LCFA-induced secretion of CCK. In fact, mice genetically lacking NEFA1 receptor were unable to increase CCK secretion after linolenic acid stimulation although this has been observed in wild-type mice[85]. Furthermore, fatty acid sensing via NEFA1R elicits secretion of incretins such as GIP and GLP-1 because of its co-localisation with these peptides in EEC. Additionally, it has been shown that substitution of the gene encoding for NEFA1R with that of β-galactosidase in mice decreases GIP and GLP-1 release in response to a fatty diet[72]. It thus seems that GPR120 and NEFA1 receptors are prominent for gut endocrine signalling, at least for CCK and incretins. Besides, LCFA were also shown to induce PYY secretion in rats and in human subjects[86–88] but the underlying mechanism is unknown and the role of LCFA receptors has not been studied. A dose-dependent secretion of PYY after fat exposure in the intestinal lumen (mostly in the ileum) as described in the CCK case is not observed[88]. However, the unsaturation number and position but not the chain length of fatty acids seem to be important for the release of GI peptides, at least for PYY or CCK. For stimulating their secretion, (i) unsaturated fatty acids are more potent than saturated ones[87], (ii) unsaturated *n*-9 (such as conjugated linoleic acid) are more potent compared with unsaturated *n*-6 (arachidonic acid) or *n*-3 (such as eicosapentanoic and DHA)[89], (iii) C_{12} (lauric acid) and C_{18} (oleic acid) have a similar effect[90].

SCFA is sensed in the lumen by NEFA2 and NEFA3 receptors (previously named as GPR43 and GPR41), which have been co-localised with PYY in EEC[91,92]. We suppose that these receptors may modulate the release of

https://doi.org/10.1017/S0029665112000110 Published online by Cambridge University Press

these peptides by EEC and may explain how fatty acid stimulates PYY secretion. The most convincing data is for the impairment of PYY secretion in NEFA3 receptor null mice[93]. Because dietary fibre generates SCFA, signalling through NEFA2 and NEFA3 receptors may thus be one of the pathways by which dietary fibre induces the release of GI peptides, at least for PYY.

Fatty acid in the cytosol and metabolism-associated signalling mechanisms

Post-absorptive signalling of fat also seems to be important for gut endocrine function. Oleoyl-ethanolamide, a derivative produced in the gut after fatty acid absorption, has been shown to induce the release of GLP-1 and GIP dependently on sensing by GPR119 receptor in the intestines of rats[75] and human subjects[94]. ApoIV, a peptide secreted in response to LCFA absorption and involved in TAG regeneration, may also contribute to CCK secretion[95]. After being absorbed, LCFA in the cytosol of intestinal cells is processed by acyl-CoA synthetase generating LCFA-CoA. In the fed state (high energy availability), LCFA is conveyed by chylomicron and mainly stored in adipocytes. During the postprandial phase characterised by a decrease of energy availability, LCFA-CoA reacts with carnitine to become an acyl-carnitine which is transported by carnitine palmitoyltransferase-1 transporter into the mitochondria. Here LCFA-CoA undergoes β-oxidation to generate malonyl-CoA which is further cleaved by malonyl-CoA decarboxylase to acetyl-CoA that enters the tricarboxylic acid cycle to produce ATP. Decrease in inward malonyl-CoA concentration in mitochondria reveals a cellular energy deficiency for ATP production that could trigger hepatic glucose production. In the opposite situation when energy is available after refeeding, cytosolic LCFA-CoA concentration increases. β-oxidation is thus inhibited inducing an increase in mitochondrial malonyl-CoA that inhibits carnitine palmitoyltransferase-1. This results in an increase in cytosolic LCFA-CoA[96] that inhibits hepatic glucose production[97]. Accordingly, hypothalamic decrease of malonyl-CoA stimulates feeding[98]. The hypothalamic energy sensor AMP-activated protein kinase may be of importance in this process because it inhibits the activity of acetyl-CoA carboxylase[99] and contributes to a decrease of malonyl-CoA level. In a mechanistic study, hypothalamic blockade of fatty acid synthase in mice ends in an increase in malonyl-CoA which decreases food intake[100]. Concentration of hypothalamic malonyl-CoA thus mediates the influence of central LCFA-CoA availability on feeding[80].

Conclusion

Taken together, current knowledge indicates that two main steps of ligand–receptor interactions are involved in the gut–brain nutrient sensing and signalling pathway. The first step is nutrient-specific 'taste' receptors or transporters located in the intestinal epithelium sensing nutrient availability in the intestinal lumen that control the release of GI regulatory peptides. The second step involves GI regulatory peptide receptors located on the vagus nerve and in the brain that control the activity of the hypothalamic and brainstem networks, respectively. According to this picture, the specific 'taste' receptors or transporters located in the gut represent a key step triggering the release of GI peptides and their subsequent effects in response to a meal[101]. The integrated activity of these receptors participates with other signals related to the nutritional state to modulate the activity of neuronal hypothalamo-brainstem networks involved in the control of gut functions, energy metabolism and food and energy intake. These receptors act as sensors of luminal nutrient availability modulating, for example, nutrient absorption and release of incretin hormones from EEC. The nutrient-derived signals recognised by specific taste receptors in the gut are monosaccharides, NEFA, free amino acids and peptides. Incretin hormones are involved as signals in the gut–brain axis, sending information to the brain on nutrient availability in the gut lumen. These different nutrients (carbohydrate, lipid and protein) are known to differently trigger GI peptide release and gut–brain signalling, and this could subsequently differently affect some of the related functional responses to feeding. The release of GI peptides appears to differently respond to the nutrient composition of meals[7,40]. It is established that CCK release is sensitive to NEFA, amino acids and peptides but not to monosaccharides, whereas the release of 5-hydroxytryptamine is sensitive to monosaccharides but not NEFA, amino acids and peptides. Moreover, 5-hydroxytryptamine and CCK are mainly released in response to glucose by EC cells and to protein and fat by I-cells at the level of the proximal intestine, whereas PYY and GLP-1 are released by L-cells in response to the three nutrients but probably with different level of sensitivity at the level of the distal intestine. These differences could modulate the nature of the signals sent to the brain; it has been observed for instance that intragastric protein hydrolysate and sucrose activate different neuronal subpopulations in the nucleus of the tractus solitary in mice[102]. Accordingly, the different nutrients and different meal compositions differently modulate the response to feeding as shown by gastric secretion, gastric and intestinal motility or the induction of satiation and satiety[61,103–106]. As a consequence, gut nutrient receptors could be pharmacologically targeted in order to stimulate an optimised GI peptide secretion profile in relation to the control of the feeding pattern.

Acknowledgements

This work was supported by AgroParisTech-INRA. The authors declare no conflict of interest. R. R. and D. T. wrote and N. D. and G. F. reviewed the paper. The authors thank Dr Nachiket A. Nadkarni for editing the manuscript.

References

1. Choi S, Lee M, Shiu AL, *et al.* (2007) Identification of a protein hydrolysate responsive G protein-coupled receptor in enterocytes. *Am J Physiol* **292**, G98–G112.
2. Hirasawa A, Tsumaya K, Awaji T, *et al.* (2005) Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat Med* **11**, 90–94.

3. Li X, Staszewski L, Xu H, *et al.* (2002) Human receptors for sweet and umami taste. *Proc Natl Acad Sci USA* **99**, 4692–4696.
4. Blevins JE & Baskin DG (2010) Hypothalamic-brainstem circuits controlling eating. *Forum Nutr* **63**, 133–140.
5. Cummings DE & Overduin J (2007) Gastrointestinal regulation of food intake. *J Clin Invest* **117**, 13–23.
6. Grill HJ & Hayes MR (2009) The nucleus tractus solitarius: a portal for visceral afferent signal processing, energy status assessment and integration of their combined effects on food intake. *Int J Obes* **33**, Suppl. 1, S11–S15.
7. Delzenne N, Blundell J, Brouns F, *et al.* (2010) Gastrointestinal targets of appetite regulation in humans. *Obes Rev* **11**, 234–250.
8. Neary MT & Batterham RL (2009) Gut hormones: implications for the treatment of obesity. *Pharmacol Ther* **124**, 44–56.
9. Moran TH & Dailey MJ (2011) Intestinal feedback signaling and satiety. *Physiol Behav* **105**, 77–81.
10. Grundy D (2006) Signalling the state of the digestive tract. *Auton Neurosci* **125**, 76–80.
11. Steinert RE & Beglinger C (2011) Nutrient sensing in the gut: interactions between chemosensory cells, visceral afferents and the secretion of satiation peptides. *Physiol Behav* **105**, 62–70.
12. Niijima A (2000) Reflex effects of oral, gastrointestinal and hepatoportal glutamate sensors on vagal nerve activity. *J Nutr* **130**, 4S Suppl., 971S–973S.
13. Joyner K, Smith GP & Gibbs J (1993) Abdominal vagotomy decreases the satiating potency of CCK-8 in sham and real feeding. *Am J Physiol* **264**, R912–R916.
14. Abbott CR, Monteiro M, Small CJ, *et al.* (2005) The inhibitory effects of peripheral administration of peptide YY(3–36) and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway. *Brain Res* **1044**, 127–131.
15. Ruttimann EB, Arnold M, Hillebrand JJ, *et al.* (2009) Intrameal hepatic portal and intraperitoneal infusions of glucagon-like peptide-1 reduce spontaneous meal size in the rat via different mechanisms. *Endocrinology* **150**, 1174–1181.
16. Greenberg D, Smith GP & Gibbs J (1990) Intraduodenal infusions of fats elicit satiety in sham-feeding rats. *Am J Physiol* **259**, R110–R118.
17. Cheung GW, Kokorovic A, Lam CK, *et al.* (2009) Intestinal cholecystokinin controls glucose production through a neuronal network. *Cell Metab* **10**, 99–109.
18. L'Heureux-Bouron D, Tome D, Rampin O, *et al.* (2003) Total subdiaphragmatic vagotomy does not suppress high protein diet-induced food intake depression in rats. *J Nutr* **133**, 2639–2642.
19. Chandrashekar J, Mueller KL, Hoon MA, *et al.* (2000) T2Rs function as bitter taste receptors. *Cell* **100**, 703–711.
20. Wong GT, Gannon KS & Margolskee RF (1996) Transduction of bitter and sweet taste by gustducin. *Nature* **381**, 796–800.
21. He W, Yasumatsu K, Varadarajan V, *et al.* (2004) Umami taste responses are mediated by alpha-transducin and alpha-gustducin. *J Neurosci* **24**, 7674–7680.
22. Liu D & Liman ER (2003) Intracellular Ca^{2+} and the phospholipid PIP2 regulate the taste transduction ion channel TRPM5. *Proc Natl Acad Sci USA* **100**, 15160–15165.
23. Bezencon C, le Coutre J & Damak S (2007) Taste-signaling proteins are coexpressed in solitary intestinal epithelial cells. *Chem Senses* **32**, 41–49.
24. Dyer J, Salmon KS, Zibrik L, *et al.* (2005) Expression of sweet taste receptors of the T1R family in the intestinal tract and enteroendocrine cells. *Biochem Soc Trans* **33**, 302–305.
25. Mace OJ, Affleck J, Patel N, *et al.* (2007) Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. *J Physiol* **582**, 379–392.
26. Rozengurt N, Wu SV, Chen MC, *et al.* (2006) Colocalization of the alpha-subunit of gustducin with PYY and GLP-1 in L cells of human colon. *Am J Physiol* **291**, G792–G802.
27. Wu SV, Rozengurt N, Yang M, *et al.* (2002) Expression of bitter taste receptors of the T2R family in the gastrointestinal tract and enteroendocrine STC-1 cells. *Proc Natl Acad Sci USA* **99**, 2392–2397.
28. Wu SV, Chen MC & Rozengurt E (2005) Genomic organization, expression, and function of bitter taste receptors (T2R) in mouse and rat. *Physiol Genomics* **22**, 139–149.
29. Burant CF, Takeda J, Brot-Laroche E, *et al.* (1992) Fructose transporter in human spermatozoa and small intestine is GLUT5. *Journal of Biol Chem* **267**, 14523–14526.
30. Cheeseman CI (1993) GLUT2 is the transporter for fructose across the rat intestinal basolateral membrane. *Gastroenterology* **105**, 1050–1056.
31. Margolskee RF, Dyer J, Kokrashvili Z, *et al.* (2007) T1R3 and gustducin in gut sense sugars to regulate expression of Na+-glucose cotransporter 1. *Proc Natl Acad Sci USA* **104**, 15075–15080.
32. Dyer J, Daly K, Salmon KS, *et al.* (2007) Intestinal glucose sensing and regulation of intestinal glucose absorption. *Biochem Soc Trans* **35**, 1191–1194.
33. Tobin V, Le Gall M, Fioramonti X, *et al.* (2008) Insulin internalizes GLUT2 in the enterocytes of healthy but not insulin-resistant mice. *Diabetes* **57**, 555–562.
34. Rozengurt E & Sternini C (2007) Taste receptor signaling in the mammalian gut. *Curr Opin Pharmacol* **7**, 557–562.
35. Gerspach AC, Steinert RE, Schonenberger L, *et al.* (2011) The role of the gut sweet taste receptor in regulating GLP-1, PYY, and CCK release in humans. *Am J Physiol Endocrinol Metab* **301**, E317–E325.
36. Kidd M, Modlin IM, Gustafsson BI, *et al.* (2008) Luminal regulation of normal and neoplastic human EC cell serotonin release is mediated by bile salts, amines, tastants, and olfactants. *Am J Physiol* **295**, G260–G272.
37. Jang HJ, Kokrashvili Z, Theodorakis MJ, *et al.* (2007) Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc Natl Acad Sci USA* **104**, 15069–15074.
38. Geraedts MC (2009) Release of satiety hormones induced by the five basic tastants is controlled by the influx of Calcium. *Gastroenterology* **36**, 136, 425.
39. Geraedts MC, Troost FJ & Saris WH (2011) Different tastants and low-caloric sweetners induce differential effects on the release of satiety hormones. *Food Chem* **129**, 8.
40. Karhunen LJ, Juvonen KR, Huotari A, *et al.* (2008) Effect of protein, fat, carbohydrate and fibre on gastrointestinal peptide release in humans. *Regul Pept* **149**, 70–78.
41. Zhao GQ, Zhang Y, Hoon MA, *et al.* (2003) The receptors for mammalian sweet and umami taste. *Cell* **115**, 255–266.
42. Nelson G, Chandrashekar J, Hoon MA, *et al.* (2002) An amino-acid taste receptor. *Nature* **416**, 199–202.
43. Chaudhari N, Landin AM & Roper SD (2000) A metabotropic glutamate receptor variant functions as a taste receptor. *Nat Neurosci* **3**, 113–119.
44. Blackshaw LA, Page AJ & Young RL (2011) Metabotropic glutamate receptors as novel therapeutic targets on visceral sensory pathways. *Front Neurosci* **5**, 40.
45. Conigrave AD, Quinn SJ & Brown EM (2000) L-amino acid sensing by the extracellular Ca^{2+}-sensing receptor. *Proc Natl Acad Sci USA* **97**, 4814–4819.

NS Proceedings of the Nutrition Society

https://doi.org/10.1017/S0029665112000110 Published online by Cambridge University Press

46. Conigrave AD, Mun HC, Delbridge L, *et al.* (2004) L-amino acids regulate parathyroid hormone secretion. *J Biol Chem* **279**, 38151–38159.
47. Conigrave AD & Brown EM (2006) Taste receptors in the gastrointestinal tract. II. L-amino acid sensing by calcium-sensing receptors: implications for GI physiology. *Am J Physiol* **291**, G753–G761.
48. Hebert SC, Cheng S & Geibel J (2004) Functions and roles of the extracellular Ca^{2+}-sensing receptor in the gastrointestinal tract. *Cell Calcium* **35**, 239–247.
49. Nakamura E, Hasumura M, Uneyama H, *et al.* (2011) Luminal amino acid-sensing cells in gastric mucosa. *Digestion* **83**, Suppl. 1, 13–18.
50. Pi M, Faber P, Ekema G, *et al.* (2005) Identification of a novel extracellular cation-sensing G-protein-coupled receptor. *J Biol Chem* **280**, 40201–40209.
51. Hundal HS & Taylor PM (2009) Amino acid transceptors: gate keepers of nutrient exchange and regulators of nutrient signaling. *Am J Physiol Endocrinol Metab* **296**, E603–E613.
52. Broer S (2008) Apical transporters for neutral amino acids: physiology and pathophysiology. *Physiology* **23**, 95–103.
53. Herrera-Ruiz D, Wang Q, Gudmundsson OS, *et al.* (2001) Spatial expression patterns of peptide transporters in the human and rat gastrointestinal tracts, Caco-2 *in vitro* cell culture model, and multiple human tissues. *AAPS Pharm Sci* **3**, E9.
54. Shen H, Smith DE & Brosius FC III (2001) Developmental expression of PEPT1 and PEPT2 in rat small intestine, colon, and kidney. *Pediatr Res* **49**, 789–795.
55. Rubio-Aliaga I & Daniel H (2002) Mammalian peptide transporters as targets for drug delivery. *Trends Pharmacol Sci* **23**, 434–440.
56. Hu Y, Smith DE, Ma K, *et al.* (2008) Targeted disruption of peptide transporter Pept1 gene in mice significantly reduces dipeptide absorption in intestine. *Mol Pharm* **5**, 1122–1130.
57. Kilberg MS, Pan YX, Chen H, *et al.* (2005) Nutritional control of gene expression: how mammalian cells respond to amino acid limitation. *Annu Rev Nutr* **25**, 59–85.
58. Chotechuang N, Azzout-Marniche D, Bos C, *et al.* (2009) mTOR, AMPK, and GCN2 coordinate the adaptation of hepatic energy metabolic pathways in response to protein intake in the rat. *Am J Physiol Endocrinol Metab* **297**, E1313–E1323.
59. Avruch J, Long X, Ortiz-Vega S, *et al.* (2009) Amino acid regulation of TOR complex 1. *Am J Physiol Endocrinol Metab* **296**, E592–E602.
60. Bensaid A, Tome D, Gietzen D, *et al.* (2002) Protein is more potent than carbohydrate for reducing appetite in rats. *Physiol Behav* **75**, 577–582.
61. Tomé D, Potier M, Fromentin G, *et al.* (2009) Comparison of the satiety effect of protein, fat and carbohydrate preloads with the same energy, volume and palatability. FASEB Meeting April 2009, Oral Communication 2009 23rd April 2009.
62. Leech CA & Habener JF (2003) Regulation of glucagon-like peptide-1 receptor and calcium-sensing receptor signaling by L-histidine. *Endocrinology* **144**, 4851–4858.
63. Hira T, Nakajima S, Eto Y, *et al.* (2008) Calcium-sensing receptor mediates phenylalanine-induced cholecystokinin secretion in enteroendocrine STC-1 cells. *FEBS J* **275**, 4620–4626.
64. Nakajima S, Hira T, Eto Y, *et al.* (2010) Soybean beta 51–63 peptide stimulates cholecystokinin secretion via a calcium-sensing receptor in enteroendocrine STC-1 cells. *Regul Pept* **159**, 148–155.
65. Cordier-Bussat M, Bernard C, Haouche S, *et al.* (1997) Peptones stimulate cholecystokinin secretion and gene transcription in the intestinal cell line STC-1. *Endocrinology* **138**, 1137–1144.
66. Cordier-Bussat M, Bernard C, Levenez F, *et al.* (1998) Peptones stimulate both the secretion of the incretin hormone glucagon-like peptide 1 and the transcription of the proglucagon gene. *Diabetes* **47**, 1038–1045.
67. Choi S, Lee M, Shiu AL, *et al.* (2007) GPR93 activation by protein hydrolysate induces CCK transcription and secretion in STC-1 cells. *Am J Physiol* **292**, G1366–G1375.
68. Darcel NP, Liou AP, Tome D, *et al.* (2005) Activation of vagal afferents in the rat duodenum by protein digests requires PepT1. *J Nutr* **135**, 1491–1495.
69. Liou AP, Chavez DI, Espero E, *et al.* (2011) Protein hydrolysate-induced cholecystokinin secretion from enteroendocrine cells is indirectly mediated by the intestinal oligopeptide transporter PepT1. *Am J Physiol* **300**, G895–G902.
70. Matsumura K, Miki T, Jhomori T, *et al.* (2005) Possible role of PEPT1 in gastrointestinal hormone secretion. *Biochem Biophys Res Commun* **336**, 1028–1032.
71. Lowe ME (1997) Molecular mechanisms of rat and human pancreatic triglyceride lipases. *J Nutr* **127**, 549–557.
72. Edfalk S, Steneberg P & Edlund H (2008) Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. *Diabetes* **57**, 2280–2287.
73. Brown AJ, Goldsworthy SM, Barnes AA, *et al.* (2003) The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem* **278**, 11312–11319.
74. Miyauchi S, Hirasawa A, Ichimura A, *et al.* (2010) New frontiers in gut nutrient sensor research: free fatty acid sensing in the gastrointestinal tract. *J Pharmacol Sci* **112**, 19–24.
75. Lauffer LM, Iakoubov R & Brubaker PL (2009) GPR119 is essential for oleoylethanolamide-induced glucagon-like peptide-1 secretion from the intestinal enteroendocrine L-cell. *Diabetes* **58**, 1058–1066.
76. Stahl A, Hirsch DJ, Gimeno RE, *et al.* (1999) Identification of the major intestinal fatty acid transport protein. *Mol Cell* **4**, 299–308.
77. Drover VA, Nguyen DV, Bastie CC, *et al.* (2008) CD36 mediates both cellular uptake of very long chain fatty acids and their intestinal absorption in mice. *J Biol Chem* **283**, 13108–13115.
78. Nassir F, Wilson B, Han X, *et al.* (2007) CD36 is important for fatty acid and cholesterol uptake by the proximal but not distal intestine. *J Biol Chem* **282**, 19493–19501.
79. Shim J, Moulson CL, Newberry EP, *et al.* (2009) Fatty acid transport protein 4 is dispensable for intestinal lipid absorption in mice. *J Lipid Res* **50**, 491–500.
80. Breen DM, Yang CS & Lam TK (2011) Gut-brain signalling: how lipids can trigger the gut. *Diabetes Metab Res Rev* **27**, 113–119.
81. Binder HJ (2010) Role of colonic short-chain fatty acid transport in diarrhea. *Annu Rev Physiol* **72**, 297–313.
82. Feinle-Bisset C, Patterson M, Ghatei MA, *et al.* (2005) Fat digestion is required for suppression of ghrelin and stimulation of peptide YY and pancreatic polypeptide secretion by intraduodenal lipid. *Am J Physiol Endocrinol Metab* **289**, E948–E953.
83. Tanaka T, Katsuma S, Adachi T, *et al.* (2008) Free fatty acids induce cholecystokinin secretion through GPR120. *Naunyn-Schmiedeberg's Arch Pharmacol* **377**, 523–527.

NS Proceedings of the Nutrition Society

84. Shah BP, Liu P, Yu T, *et al.* (2011) TRPM5 is critical for linoleic acid-induced CCK secretion from the enteroendocrine cell line, STC-1. *Am J Physiol Cell Physiol* **302**, 200–209.
85. Liou AP, Lu X, Sei Y, *et al.* (2011) The G-protein-coupled receptor GPR40 directly mediates long-chain fatty acid-induced secretion of cholecystokinin. *Gastroenterology* **140**, 903–912.
86. Dailey MJ, Tamashiro KL, Terrillion CE, *et al.* (2010) Nutrient specific feeding and endocrine effects of jejunal infusions. *Obesity* **18**, 904–910.
87. Maljaars J, Romeyn EA, Haddeman E, *et al.* (2009) Effect of fat saturation on satiety, hormone release, and food intake. *Am J Clin Nutr* **89**, 1019–1024.
88. Maljaars PW, Symersky T, Kee BC, *et al.* (2008) Effect of ileal fat perfusion on satiety and hormone release in healthy volunteers. *Int J Obes (2005)* **32**, 1633–1639.
89. Hand KV, Bruen CM, O'Halloran F, *et al.* (2010) Acute and chronic effects of dietary fatty acids on cholecystokinin expression, storage and secretion in enteroendocrine STC-1 cells. *Mol Nutr Food Res* **54**, Suppl. 1, S93–S103.
90. Feltrin KL, Little TJ, Meyer JH, *et al.* (2008) Comparative effects of intraduodenal infusions of lauric and oleic acids on antropyloroduodenal motility, plasma cholecystokinin and peptide YY, appetite, and energy intake in healthy men. *Am J Clin Nutr* **87**, 1181–1187.
91. Karaki S, Mitsui R, Hayashi H, *et al.* (2006) Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. *Cell Tissue Res* **324**, 353–360.
92. Tazoe H, Otomo Y, Karaki S, *et al.* (2009) Expression of short-chain fatty acid receptor GPR41 in the human colon. *Biomed Res* **30**, 149–156.
93. Samuel BS, Shaito A, Motoike T, *et al.* (2008) Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci USA* **105**, 16767–16772.
94. Hansen KB, Rosenkilde MM, Knop FK, *et al.* (2011) 2-Oleoyl glycerol is a GPR119 agonist and signals GLP-1 release in humans. *J Clin Endocrinol Metab* **96**, E1409–E1417.
95. Glatzle J, Darcel N, Rechs AJ, *et al.* (2004) Apolipoprotein A-IV stimulates duodenal vagal afferent activity to inhibit gastric motility via a CCK1 pathway. *Am J Physiol Regul Integr Comp Physiol* **287**, R354–R359.
96. Ruderman NB, Saha AK, Vavvas D, *et al.* (1999) Malonyl-CoA, fuel sensing, and insulin resistance. *Am J Physiol* **276**(1 Pt 1), E1–E18.
97. Wang PY, Caspi L, Lam CK, *et al.* (2008) Upper intestinal lipids trigger a gut-brain-liver axis to regulate glucose production. *Nature* **452**, 1012–1016.
98. Hu Z, Dai Y, Prentki M, *et al.* (2005) A role for hypothalamic malonyl-CoA in the control of food intake. *J Biol Chem* **280**, 39681–39683.
99. Kahn BB, Alquier T, Carling D, *et al.* (2005) AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab* **1**, 15–25.
100. Loftus TM, Jaworsky DE, Frehywot GL, *et al.* (2000) Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. *Science* **288**, 2379–2381.
101. Janssen S, Laermans J, Verhulst PJ, *et al.* (2011) Bitter taste receptors and alpha-gustducin regulate the secretion of ghrelin with functional effects on food intake and gastric emptying. *Proc Natl Acad Sci USA* **108**, 2094–2099.
102. Schwarz J, Burguet J, Rampin O, *et al.* (2010) Three-dimensional macronutrient-associated Fos expression patterns in the mouse brainstem. *PloS One* **5**, e8974.
103. Brooks FP (1985) Effect of diet on gastric secretion. *Am J Clin Nutr* **42**, 5 Suppl., 1006–1019.
104. Faipoux R, Tome D, Bensaid A, *et al.* (2006) Yeast proteins enhance satiety in rats. *J Nutr* **136**, 2350–2356.
105. Faipoux R, Tome D, Gougis S, *et al.* (2008) Proteins activate satiety-related neuronal pathways in the brainstem and hypothalamus of rats. *J Nutr* **138**, 1172–1178.
106. Nefti W, Chaumontet C, Fromentin G, *et al.* (2009) A high-fat diet attenuates the central response to within-meal satiation signals and modifies the receptor expression of vagal afferents in mice. *Am J Physiol Regul Integr Comp Physiol* **296**, R1681–R1686.

https://doi.org/10.1017/S0029665112000110 Published online by Cambridge University Press