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Review: Chemosensing of nutrients and non-nutrients in the human and porcine gastrointestinal tract

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The gastrointestinal tract (GIT) is an interface between the external and internal milieus that requires continuous monitoring for nutrients or pathogens and toxic chemicals. The study of the physiological/molecular mechanisms, mediating the responses to the monitoring of the GIT contents, has been referred to as chemosensory science. While most of the progress in this area of research has been obtained in laboratory rodents and humans, significant steps forward have also been reported in pigs. The objective of this review was to update the current knowledge on nutrient chemosensing in pigs in light of recent advances in humans and laboratory rodents. A second objective relates to informing the existence of nutrient sensors with their functionality, particularly linked to the gut peptides relevant to the onset/offset of appetite. Several cell types of the intestinal epithelium such as Paneth, goblet, tuft and enteroendocrine cells (EECs) contain subsets of chemosensory receptors also found on the tongue as part of the taste system. In particular, EECs show specific co-expression patterns between nutrient sensors and/or transceptors (transport proteins with sensing functions) and anorexigenic hormones such as cholecystokinin (CCK), peptide tyrosine tyrosine (PYY) or glucagon-like peptide-1 (GLP-1), amongst others. In addition, the administration of bitter compounds has an inhibitory effect on GIT motility and on appetite through GLP-1-, CCK-, ghrelin- and PYY-labelled EECs in the human small intestine and colon. Furthermore, the mammalian chemosensory system is the target of some bacterial metabolites. Recent studies on the human microbiome have discovered that commensal bacteria have developed strategies to stimulate chemosensory receptors and trigger host cellular functions. Finally, the study of gene polymorphisms related to nutrient sensors explains differences in food choices, food intake and appetite between individuals.

Keywords: nutrient receptors, transceptors, pigs, enteroendocrine system, gut peptides

Implications

How the gastrointestinal tract senses the arrival of dietary nutrients and non-nutrients (e.g. toxins) has a tremendous impact on the hunger–satiety cycle. Nutrient sensing is mediated by the activation of taste receptors or other sensors/transporters present in the intestinal epithelium associated with the enteroendocrine system. For example, the excess of specific non-limiting dietary amino acids in pigs has the capacity to strongly trigger satiating signals through chemosensory mechanisms (Muller and Roura, unpublished). In the future, standard feed formulation guidelines in farm animals (including pigs) will have to include not only essential-limiting amino acids but the wider array of dietary amino acids as well. A full understanding of these mechanisms is essential to develop dietary strategies to optimize feed intake in farm animals such as the pig.

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Introduction

Nutritional chemosensing is the scientific discipline studying how nutrients are perceived in biological systems including genomic, metabolic, physiological and behavioural mechanisms (Roura *et al*., 2016). The molecular mechanisms of oral nutrient and non-nutrient sensing involve a large repertoire of receptors including taste receptors (TRs). The activation of TRs trigger the depolarization of the sensory cell in the tongue and the stimulation of the gustatory cortex of the brain mediated by the signalling of the cranial nerves VII, IX and X (Barretto *et al*., 2015). In addition, the mechanisms of nutrient perception discovered in the oral cavity have also been described outside the oral cavity as part of the enteroendocrine system (EES) mediating the hunger–satiety cycle (reviewed by Steensels and Depoortere, 2018). In the intestinal epithelium, there are several cell types, such as enterocytes, enteroendocrine cells (EECs), tuft, Paneth, goblet, microfold and cup cells, which play a key role reporting

the luminal content to the brain (Depoortere, 2014). These mechanisms were originally studied in humans and laboratory rodents; however, in recent reports homologous mechanisms have been uncovered in pigs (reviewed by Roura and Fu, 2017; Roura and Foster, 2018).

In addition, some nutrient transporters seem to play a dual role meaning that the main role of transporting might be coupled to nutrient-sensing signalling. These transporters have been referred to as 'transceptors' (Reimann *et al.*, 2008; Poncet and Taylor, 2013). Sensory functions of nutrient transporters in and outside the oral cavity are increasingly being recognized in mammalian species (Diallinas, 2017; Roura and Foster, 2018; Steensels and Depoortere, 2018). The molecular mechanisms of oral nutrient sensing and transporters are complex and imply a high degree of specificity to each nutrient type. This review aims at summarizing the current knowledge on nutrient (carbohydrates, proteins and lipids) and non-nutrient (bitter or bacterial compounds) chemosensing and the mediation of appetite-regulating gut peptides in pigs, presented using the progress obtained in humans and laboratory rodents as a reference. Novel research avenues on 'microbial and parasite sensing' have been highlighted in the 'Microbial and parasite sensing . . . ' section of the review.

Carbohydrate sensing

Carbohydrate sensing has been related to two taste-like types referred as sweet and starchy tastes in humans (Aji *et al.*, 2019). On the one hand, sweet taste has evolved around mono-, di- and tri-saccharides (simple sugars), not only in humans but also in other mammalian species including pigs (Sclafani, 1987; Glaser *et al.*, 2000; Lapis *et al.*, 2014; Low *et al.*, 2017; Roura and Fu, 2017). On the other hand, starch is the primary carbohydrate source in pigs. In recent years, starch-related sweet taste has gained relevance as part of the dietary nutrient-sensing mechanisms in the oral cavity. Despite a short contact time with starch in the mouth, salivary alpha-amylase has the potential to elicit sweet taste in humans by releasing maltose and maltotriose (Aji *et al.*, 2019).

However, the sensing of complex carbohydrates is independent of sweet taste as described in laboratory rodents (Sclafani, 1987). Lapis *et al.* (2014) demonstrated the taste of glucose was correlated with sucrose but not with the sensing of complex carbohydrates. Pigs were also reported to sense complex carbohydrates from hydrolysed corn starch (Roura *et al.*, 2013).

Carbohydrate sensors and transceptors in the gastrointestinal tract

Most mammalian species (except strict carnivores) have a very conserved mechanism of simple sugar perception (related to sweet taste in humans). Table 1 summarizes the main receptors and transporters known to be involved in sensing sugars in the gastrointestinal tract (GIT) in humans and pigs. Among other potential receptors, simple carbohydrates sensing involves a heterodimer of two G-protein-coupled receptors (GPCRs) known as taste receptor type 1 member 2 and member 3 (TAS1R2 and TAS1R3, respectively) (Bachmanov and Beauchamp, 2007). In addition, a TAS1R2/TAS1R3-independent sensing of monosaccharides (e.g. glucose and fructose) has been recently described in the oral cavity. The system was related to the glucose transporters/co-transporters (GLUTs) and sodium-dependent glucose transporter type 1 and 2 (SGLT1/2), and the brush border enzymes present in the apical membrane of some taste sensory cells (Glendinning *et al.*, 2015; Sukumaran *et al.* 2016). An analogous system has been previously described in the small intestine (Cheng *et al.*, 2014; Zhang *et al.*, 2015). In addition, the stimulation of the TAS1R sweet receptor dimer seemed to upregulate SGLT1 to facilitate glucose uptake in the intestine (Mace *et al.*, 2007; Margolskee *et al.*, 2007). GLUT5 has also been reported to influence glucagon-like peptide-1 (GLP-1) release from enteroendocrine K-cells (Douard and Ferraris, 2008). However, potential dual roles for other sugar transporters/sensors known to be expressed in the GIT (i.e. K_{ATP} channel, SGLT2, GLUT2 or GLUT5) have not been reported to date (Table 1). Some of these molecular mechanisms have also been described in pigs (Roura and Fu, 2017). The identification of putative receptors responsible for the sensing of starch and glucose polymers remains elusive to date in mammalian species.

Carbohydrates sensors and the enteroendocrine system

The presence of simple sugars in the GIT activates the expression and stimulation of TAS1Rs in EECs which, in turn, release gut peptides relevant to the orchestration of the hunger–satiety cycle (Rozengurt *et al.*, 2006). The main hormones involved in this response include cholecystokinin (CCK), peptide tyrosine tyrosine (PYY) and GLP-1 (Badman and Flier, 2005). These hormones are known to regulate energy and glucose metabolism by modulating the homoeostatic and food reward systems in the brain implicated in hunger and satiety (Berridge and Robinson, 1998). In particular, carbohydrate sensing mediated by TAS1R2/TAS1R3, SGLT1 and/or the K_{ATP} has been described on L-cells and K-cells known to secrete GLP-1 and glucose insulinotropic peptide (GIP), respectively (Steensels and Depoortere, 2018). The expression and co-localization of TAS1R2, TAS1R3 and transceptor SGLT1 in L-cells has been related to GLP-1 secretion in humans and rodents (Jang *et al.*, 2007; Steinert *et al.*, 2011a; Gerspach *et al.*, 2011). In addition, sugar sensors are found in human stomach, expressed in endocrine P/D1 cells (also referred to X/A cells in lab rodents) and inhibit the release of the hunger hormone ghrelin (Wang *et al.*, 2019). However, the effect of glucose on GLP-1 and PYY release could be overruled or potentiated by other nutrients such as proteins or fats (Gerspach *et al.*, 2011). Interestingly, artificial sweeteners showed no effect on GLP-1 *in vivo* in rodents and humans, suggesting that they may not induce physiological effects in the GIT (Steinert *et al.*, 2011b; Steensels *et al.*, 2016).

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Table 1. *Main simple carbohydrates receptors and transporters known to be involved in GIT sensing in humans and pigs*[1]

Nutrient	Gene	Receptor/transporter	Cell-type expression in gut tissues	GI peptides secreted	References[2]
Gluc, Mal, Suc, Fru, sugar alcohols	*T1R2/T1R3*	Sweet taste receptor	Taste buds, X/A cell, enteroendocrine L-cell and K-cells, pancreatic β-cells, tuft cells, Paneth cells L-cell	GIP, GLP-1, PYY,	Li *et al.*, 2002; Gerspach *et al.*, 2011; Moran *et al.*, 2010a
Gluc, Gal	*SGLT1/SGLT3*	Sweet taste receptor, glucose/galactose transporter (SGLT1) and glucose sensor (SGLT3)	Taste buds, apical membrane of enterocytes, X/A cell, L-cells, K-cell, pancreatic α-cells and SGLT3 in enteric nervous system	GIP, GLP-1	Wrigth *et al.*, 2011; Röder *et al.*, 2014; Suga *et al.*, 2019; Moran *et al.*, 2010
Gluc, GalFru, Man, Glucos	*GLUT2*	Membrane transporter	Pancreatic β -cells, K-cells, L-cells, enterocytes	Glucagon, GLP-1, Insulin	Marty *et al.*, 2006; Zuo *et al.*, 2010; Mueckler and Thorens, 2013; Fournel *et al.*, 2016; Seino *et al.*, 2016
Gluc, Glucos	*GLUT4*	Membrane transporter	T1r3-positive taste cells	-	Yee *et al.*, 2011; Zhang *et al.* 2016
Gluc, Fru, Gal	*GLUT5*	Membrane transporter	Apical membrane of enterocytes	-	Cottrell *et al.*, 2006; Douard and Ferraris, 2008
Gluc; Fru	*GLUT7*	Membrane transporter	Small intestine, colon	-	Cheeseman, 2008; Vigors *et al.*, 2016
Gluc, Fru	*GLUT9*[3]	Urate, glucose sensor	Small intestine	-	Xu*et al.*, 2016; Bu *et al.*, 2017
Gluc	K_{ATP} *channel*	Glucose sensor	Pancreatic β-cells, L-cells and K-cells	GIP, GLP-1, Insulin	Reimann and Gribble, 2002; McTaggart *et al.*, 2010

GIT = gastrointestinal tract; GI = gastrointestinal; GIP = glucose insulinotropic peptide; GLUT = glucose transporter; PYY = peptide YY; SGLT = sodium–glucose cotransporter 1; T1R = taste receptor family 1; K_{ATP} channel = ATP-sensitive K^+ channel; GLP-1 = glucagon-like peptide 1; Fru = fructose; Gluc = glucose; Gal = galactose; Man = mannose; Mal = maltose; Suc = sucrose; Glucos = glucosamine.

[1] All the receptors and transporters presented in the table are relevant to humans and pigs except if noted with the superscript 3.

[2] Table references are provided in Supplementary Material S1. Note: some references to laboratory rodent research have been used to illustrate the discovery or proof of the GIT-related function of some genes.

[3] No literature evidence of the functionality of this gene has been found in pigs.

In pigs, Moran *et al.* (2010a and 2010b) found that dietary carbohydrates or saccharin enhanced SGLT1 expression in small intestine epithelial cells including L and K cells resulting in an increased glucose absorption. In addition, L and K cells co-expressed pTas1r2/pTas1r3, SGLT1 and GIP and GLP-1. Thus, SGLT1 was shown to be the main route of absorption of dietary sugars and that the increased expression of SGLT1 in epithelial cells was mediated by the stimulation of pTas1rs in pigs (Moran *et al.*, 2010b).

Gene polymorphisms in carbohydrate sensing

Based on population genomic analyses, 18 single-nucleotide polymorphisms (SNPs) (of which 10 were non-synonymous – ns – that is, causing a change in the amino acid (AA) sequence of the receptor) have been identified in TAS1R2 (Kim *et al.*, 2006). TAS1R2 variants have been associated with higher sucrose taste thresholds and dietary sugar intake (Eny *et al.*, 2010) or to lower carbohydrate intake (Ramos-Lopez *et al.*, 2016). In addition, Dias *et al.* (2015) found that the functional impact of another TAS1R2 polymorphism was body mass index (BMI) dependent – that is, high sucrose thresholds and sugar intake found in overweight individuals (BMI>25) but not in normal-weight individuals (BMI<25). Furthermore, low compared to high sweet taste sensitivity volunteers consumed a higher amount of energy from a buffet meal, implying a strong involvement of TAS1R2 allelic variants on food choices (Han *et al.*, 2017). In the same study, low sweet sensitivity was related to high salivary leptin. Similarly, a high oral sensitivity to the taste of complex carbohydrates (maltodextrin and oligofructose) was associated with higher consumption of energy and starch and waist circumference (Low *et al.*, 2017). Regarding genetic polymorphisms in pigs, the studies conducted to date have not reported potential pTas1r2 variants because the gene was not annotated in the pig genome at the time the studies were conducted (Da Silva *et al.*, 2014; Clop *et al.*, 2016).

Protein/amino acid sensing

Dietary protein, as a source of AA, plays a fundamental role in growth and development. Of the 20 proteinogenic AAs needed for protein synthesis in eukaryotic cells, a few cannot be metabolically synthesized '*de novo*' from other carbon and nitrogen sources within the cells, and need to be consumed as part of the diet. Thus, optimal growth and development in pigs requires a balanced supply of these so-called dietary essential AAs; one of the key aspects in current pig feed formulation practices. Failure to supply a balanced diet in terms of essential AA results in deficient growth and development and ultimately death. Thus, it is not surprising that a wide array of AAs and peptide sensors exist in mammalian species. In humans, the oral sensing of dietary AA was originally related to glutamate (and aspartate) and defined as the umami taste (Ikeda, 1909). Other AAs sensed include aromatic AA (e.g. L-Phe), basic AA (L-Arg) and dietary peptides (Zhang *et al.*, 2014). However, in other mammals such as laboratory rodents and pigs, the oral/umami sensing of AA involves several L-AAs (Tinti *et al.*, 2000; Roura *et al.*, 2011).

Amino acid sensors and transceptors in the gastrointestinal tract

Table 2 shows the main receptors and transporters known to be involved in AA sensing in the GIT in humans and pigs. The umami taste receptor is a GPCR heterodimer: TAS1R1/TAS1R3 (Nelson *et al.*, 2002). In addition, the metabotropic glutamate receptors (particularly mGluR1 and mGluR4) have also been related to glutamate sensing in humans, in and outside the oral cavity (San Gabriel and Uneyama, 2013). Other AA sensors have been identified including the calcium sensing receptor (CaSR, sensing basic AA and Ca2+ as a heterotrophic cooperative enhancer) and GPRC6A (sensing aromatic AA) (Zhang *et al.*, 2014; Steensels and Depoortere, 2018). CaSR acts in concert with GPRC6A and are found expressed in D-, G- and L-cells (Haid *et al.*, 2012). Finally, di- and tripeptides are sensed by GPR92/93. Similar to previous receptors, AA sensors are also widely expressed throughout the GIT in humans, lab rodents and pigs (Wellendorph *et al.*, 2010; Roura and Foster, 2018) (Table 2).

There is a complex and highly specific network of AA and peptide intestinal transporters belonging to the solute carrier (SLC) family. A detailed description of these transporters can be found elsewhere (Broer, 2008). However, the evidence of any of these transporters to function as AA sensors remains to be fully studied.

Amino acids and the enteroendocrine system

In the GIT, the stimulation of the umami heterodimer and the CaSR have been associated with the secretion of CCK, ghrelin and GLP-1 (Liou *et al.*, 2011a; Diakogiannaki *et al.*, 2013; Vancleef *et al.*, 2015). In addition, GPR92/93 has been reported in stomach G-cells and STC-1 cells responding to a protein hydrolysate by releasing CCK (Choi *et al.*, 2007; Rettenberger *et al.*, 2015).

Similar to the TAS1R-independent mechanisms of sweet taste perception, the AA sensing also seems to partially rely on AA transceptors as an alternative pathway to signal responses through EEC. Di/tripeptide uptake in L cells occurs via peptide transporter 1 (PEPT1) and results in subsequent basolateral activation of the CaSR and GLP-1 release (Diakogiannaki *et al.*, 2013; Daniel and Zietek, 2015; Modvig *et al.*, 2019). Another potential example of AA transceptor is the sodium-dependent neutral AAs transporter 2 (SNAT2) involved in GLP-1 secretion (Reimann *et al.*, 2006; Young *et al.*, 2010). A large number of additional AA transporters (e.g. the SLC family) are known to be expressed in the GIT but, as indicated previously, their potential role as transceptors has not been fully described (Broer, 2008). In pigs, the first fully functional taste receptor gene to be sequenced, cloned and expressed in a cell reporter system was the umami heterodimer pTas1r1/pTas1r3 (Humphrey *et al.*, 2009; Tedo Perez, 2009; Roura *et al.*, 2011). The results indicated that the umami taste in pigs was tuned to 8 L-AA (Ala, Asn,

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Table 2. *Main AA receptors and transceptors known to be involved in GIT sensing in humans and pigs*[1]

AA and peptides	Gene	Receptor/transporter	Cell-type expression in the GIT	GI peptides secreted	References[2]
L-AA[3]	*T1R1/T1R3*	Umami taste receptor	Taste buds, L and K-cells	CCK, Ghrelin	Steensels and Depoortere, 2018
Peptides, Lysophosphatidic acid	*GPR92 (GPR93/LPAR5)*	Peptone and LPA sensor	Gustatory sensory cells, G-cells, D-cells and GIT lymphocytes	CCK, Gastrin, Ghrelin	Haid *et al.*, 2012 and 2013; Kotarsky *et al.*, 2006
L-Phe and L-Trp, peptone	*CaSR,*	Sensing of aromatic AA	Taste buds tongue, K-cells, G-cells, I-cells, L-cells, D-cells, SCFA-surface cells large intestine.	CCK, Gastrin, GLP-1, GIP, Ghrelin	Vancleef *et al.*, 2015; Wang *et al.*, 2018; Zhao *et al.*, 2018; Modvig *et al.*, 2019
L-α-amino acids and divalent cations	*GPRC6A*	AA sensor	G-cells, D-cells, L-cells, pancreas, liver and gallbladder	GLP-1	Haid *et al.*, 2012; Oya *et al.*, 2013; Depoortere, 2014
L-Glutamic	*mGluR4, mGluR1*	L-glutamate receptor	Taste buds and enterocytes	-	Chaudhari *et al.*, 2000; Toyono *et al.*, 2003; Da Silva *et al.*, 2014
di-tripeptides	*PepT1, 2*	Peptide transport into cell	Apical microvilli enterocytes in small intestine	GLP-1	Vigors *et al.*, 2016; Modvig *et al.*, 2019

AA = amino acid; GIT = gastrointestinal tract; GI = gastrointestinal; LPA = lysophosphatidic acid; CaSR = calcium-sensor receptor; CCK = cholecystokinin; L-AA = L isomer of amino acids; GPCRs = G-protein-coupled receptors; SCFA = short-chain fatty acid; GLP-1 = glucagon-like peptide 1; GIP = glucose-dependent insulinotropic peptide; mGluRs = metabotropic glutamate receptors; PepT1,2: peptide transporter 1 and 2; T1R = taste receptor family 1.

[1] All the receptors and transporters presented in the table are relevant to humans and pigs.

[2] Table references are provided in Supplementary Material S1. Note: some references to laboratory rodent research have been added to illustrate the discovery or proof of the GIT-related function of some genes.

[3] Refers to L-AA stimulating the umami taste receptor dimer in humans (glutamic and aspartic acids) or pigs (Ala, Asn, Asp, Glu, Gln, Pro, Ser and Thr) (*source*: Roura *et al.*, 2011).

Asp, Glu, Gln, Pro, Ser and Thr) (Roura *et al.*, 2011). The expressions of the porcine metabotropic glutamate receptors (mGluR1 and mGluR4) and other AA and peptone receptors (i.e. CaSR, GPRC6A and GPR92) have also been reported more recently in pig tongue and stomach epithelia (Haid *et al.*, 2012; Da Silva *et al.*, 2014). In addition, the AA receptors involved in sensing protein breakdown products were identified in G-cells and D-cells in pigs (Haid *et al.*, 2012). Finally, several AA transporters of the SLC family have been identified in the pig GIT; however their potential role as sensors has not been addressed (Vigors *et al.*, 2014).

Gene polymorphisms in amino acid sensing

In humans, 17 SNPs (14 ns) and 12 SNPs (6 ns) were reported for TAS1R1 and TAS1R3, respectively (Kim *et al.*, 2006). These polymorphisms have been associated with a lower ability to taste glutamate (Chen *et al.*, 2009) and with specific food choices (Han *et al.*, 2018). In particular, the research published from Han *et al.* (2018) reported that human carriers of one of the TAS1R1 SNPs consumed more fat and calories from a buffet meal. In addition, Raliou *et al.* (2009) showed that mGluR1 polymorphisms contributed to a lack of sensitivity to glutamate. Genetic variants in other AA sensors (i.e. CaSR and GPRC6A) have also been reported; however, the physiological impact of this variation is currently unknown.

In pigs, an SNP analysis of 79 pig genomes (belonging to 14 different breeds) revealed 13 (5 ns and 1 stop-lost) and 9 (1 ns) polymorphisms in pTasS1r1 and pTas1r3, respectively (Da Silva *et al.*, 2014). The research also showed several SNPs for the other AA sensors: 22 (2 ns), 6 (3 ns), 16 (1 ns) and 28 (2 ns) for CaSR, GPRC6A, mGluR1 and mGluR4, respectively. Clop *et al.* (2016) identified 31 (including 1 splice, 1 stop-gained and 1 stop lost, 3 frame shifts and 4 moderate impact) pTas1r1 variants and 14 (including 1 stop gained and 1 moderate impact) pTas1r3 variants. In addition, they identified an mGluR1 SNP linked to umami taste, feed intake and growth. However, the incidence of SNP in AA sensors compared to the bitter sensing system was very low (Da Silva *et al.*, 2014). This limited number of ns SNPs may indicate that AA receptor/transceptor functions are highly conserved across individuals and across pig breeds.

Lipid/fatty acid sensing

Fats are an essential dietary energy source that play a key role in gut hormone release (Hara *et al.*, 2014). Triglycerides, the main dietary fat source, are digested by lipases releasing free fatty acids (FFAs) and monoacylglycerides.

Fatty acid sensors and transceptors in the gastrointestinal tract

The chemosensory system for fats has evolved mainly around the sensing of FFAs and consists of an array of nine receptors (FFARs) and transceptors featuring a degree of specificity based on chain length (Table 3). In particular, the main

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Table 3. *Main FFA receptors and transceptors known to be involved in GIT sensing in humans and pigs*[1]

Nutrient	Gene	Function	Cell-type expression in the GIT	GI peptides secreted	References[2]
C1-C6	*FFAR2 (GPR43)*	FFA taste receptor, and FFA sensing	Endocrine L-cells, pancreatic α-cells and β-cells, gastric brush cells, leukocytes in the lamina propria of the small intestine	Ghrelin, GLP-1 and PYY,	Kaji *et al.*, 2011; Colombo *et al.*, 2012; Engelstoft *et al.*, 2013; Brooks *et al.*, 2017
C1-C6	*FFAR3 (GPR41)*	FFA taste receptor, and FFA sensing	Taste buds, L-cells, I-cells, pancreatic α-cells and β-cells, gastric brush cells, neurons in submucosal and mesenteric ganglia	GLP-1 and PYY	Tazoe *et al.*, 2009; Nøhr*et al.*, 2013; Li *et al.*, 2014; Chambers *et al.*, 2015
C4	*MCT1 (SLC16A1)*	Butyrate transporter	Caco-2 cells colon	–	Haenen *et al.*, 2013; Stumpff, 2018
C9-C14	*GPR84*	Regulation of systemic energy metabolism, lipid sensor	Taste buds, oral granulocytes, G-cells (stomach), colon, liver		Da Silva *et al.*, 2014; Liu *et al.*, 2018; Widmayer *et al.*, 2017
C10-C22, saturated and unsaturated	*FFAR1 (GPR40)*	FFA taste receptor[3] and FFA sensing	Taste buds and L-cells, I-cells, pancreatic β-cells	CCK, insulin	Itoh *et al.*, 2003; Liou *et al.*, 2011b ; Da Silva *et al.*, 2014; Chen *et al.*, 2017
C12-C22, saturated and unsaturated	*FFAR4 (GPR120)*	FFA taste receptor, and FFA sensing	Taste buds, K-cells, L-cells, pancreatic islet δ-cells and Kupffer cells	GLP-1, GIP, CCK, ghrelin, glucagon, insulin	Colombo *et al.*, 2012; Gong*et al.*, 2013; Ichimura*et al.*, 2014; Iwasaki *et al.*, 2015
Long-chain FA	*FABP2*	FA transporter	Enterocytes K-cells	GIP	Besnard *et al.*, 2002; Vigors *et al.*, 2016
Long-chain FA	*FATP4*	FA transporter	Small intestine enterocytes,	CCK, secretin	Stahl *et al.*, 1999; Zong *et al.*, 2018
Long-chain FA	*CD36*	FA translocase, regulation of fat sensing	Apical side of lingual taste bud cells. Brush border membrane of enterocyte small intestine	GLP-2	Laugerette *et al.*, 2005; Yamamoto *et al.*, 2012; Vigors *et al.*, 2016
Propionate	*OLFR78*[4]	FA sensing	Colonic L-cells	PYY	Fleischer *et al.*, 2015
Butyrate	*OR51E1*	FA sensing	Stomach, pyloric, duodenal, jejunal, ileal, caecal, colonic and rectal mucosae L-cells	GLP-1, PYY	Priori *et al.*, 2015; Han *et al.*, 2018
2-monoglycerides	*GPR119*[4]	Enteroendocrine lipid sensor	L-cells, β-cells	GLP-1, PYY, insulin	Soga *et al.*, 2005; Overton *et al.*, 2006, Kogure *et al.*, 2011
Bile acids	*GPBAR1 (TGR5)*	Cell surface receptor for bile acids	Liver sinusoidal endothelial cells, gall bladder epithelial cells, kupffer cells, enteric neurons and cells	PYY, GLP-1	Poole *et al.*, 2010; Jain *et al.*, 2012; Dehmlow *et al.*, 2013

FFA = free fatty acids; GIT = gastrointestinal tract; GI = gastrointestinal; FFARs = free fatty acid receptors; CCK = cholecystokinin; CD36 = cluster of differentiation 36; FABP2 = fatty acid binding protein 2; FATP4 = fatty acid transporter 4; SLC16A1 = solute carrier family 16 member; GLP-1 = glucagon-like peptide 1; GIP = glucose insulinotropic peptide; GLP-1 = glucagon-like peptide 1; GPBAR1 = G-protein-coupled bile receptor; TGR5 = Takeda G-protein-coupled receptor 5; GPR = G-protein-coupled receptor; MCT1 = monocarboxylate transporter 1; OLFR78 = olfactory receptor 78; PYY = peptide YY

[1] All the receptors and transporters presented in the table are relevant to humans and pigs except if noted with the superscript 4.

[2] Table references are provided in Supplementary Material S1.

[3] Refers to the oral sensation elicited by free fatty acids (Note: to date, the FFA sensing has not achieved full recognition as a primary taste type by the sensory science community).

[4] No literature evidence of the existence or functionality of these genes has been found in pigs.

ligands for FFAR2 and FFAR3 and olfactory receptor OLFR78 are short-chain fatty acids (SCFAs). The receptors FFAR1 and GPR84 showed the highest affinity for medium-chain fatty acids (MCFAs)(Wang *et al.* 2006; Liu *et al.*, 2018), whereas FFAR4 (also kwon as GPR120) and fatty acid (FA)-binding protein 2 (FABP2), FA transport protein 4 (FATP4) and cluster of differentiation 36 (CD36) have been characterized as receptors for long-chain fatty acids (LCFAs) (Bachmanov and Beauchamp, 2007; Mattes, 2011). In addition, GPR119 has been proposed as a putative receptor for endogenous lipids containing oleic acid (e.g. oeloylethanolamide) and 2-monoacylglycerol (Hansen *et al.*, 2012).

Fatty acids and the enteroendocrine system

The receptors FFAR1 and FFAR4 are present throughout the GIT found in EECs. The uptake of dietary FFAs is slow (compared to sugars and AA) and requires bile acids secreted in the duodenum. In contrast, FFAR2, FFAR3 and OLFR78 are preferentially expressed in the colon, where abundant SCFAs are produced resulting from bacterial fermentation (Canfora *et al.* 2015; Fleischer *et al.*, 2015). GPR84 has been reported in mouse gastric mucosa (Widmayer *et al.*, 2017). GPR119 expression has been associated with EECs (L-cells) and pancreatic cells (Overton *et al.* 2008; Lan *et al.*, 2009; Hansen *et al.*, 2012).

On the one hand, intragastric administration of dietary oral gavage of LCFA has been reported to increase the orexigenic (appetite) hormone ghrelin secretion presumably through the stimulation of FFAR4 (Janssen *et al.* 2012). In addition, the activation of FFAR2-expressing gastric X/A-cells by SCFA inhibited ghrelin (Engelstoft *et al.* 2013). Short-chain fatty acid can reach the stomach through the portal vein (Morrison and Preston, 2016). This may be indicative of an excessive fermentation occurring in the lower GIT which is consistent with an anorexegenic (satiating) response. On the other hand, some FFARs have also been related to anorexigenic events associated with CCK and/or GLP-1 and GIP. An acute oral dose of butyrate increased GLP-1 and PYY levels in mice, presumably through FFAR3 (Lin *et al.* 2012). The expression of GPR84 in X/A-like ghrelin cells and surface cells suggests an important role of MCFA in the developing gastric mucosa of suckling mice (Widmayer *et al.*, 2017). In addition, SCFA olfactory receptor OLFR78 and GLP-1 and PYY co-express in murine colonic L-cells (Pluznick, 2014; Fleischer *et al.*, 2015). Furthermore, GPR119 ligands (i.e. monoglycerides) triggered GLP-1 secretion from intestinal primary cultures, particularly from colon (Moss *et al.*, 2016). Fatty acid transceptors CD36 and FATP4 have been also reported to mediate lipid-induced gut hormone secretion (Sundaresan *et al.*, 2013; Poreba *et al.*, 2012).

In pigs, De Jager *et al.* (2013) reported the expression of FFAR1, FFAR2, FFAR3, FFAR4 and GPR84 in circumvallate papillae. In addition, Da Silva *et al.* (2014) revealed a very low incidence of allelic variants across FFARs and GPR84 compared to other TR genes such as the TAS2R family (bitter taste) indicating that FFARs were highly conserved in pigs.

The FFARs expression pattern described in pigs evidenced some differences compared to humans. In particular, FFAR2 and FFAR3 were predominantly found in the distal small intestine (Haenen *et al.*, 2013) while FFAR4 in colon (Colombo *et al.*, 2012; van der Wielen *et al.*, 2014). It is tempting to speculate that these findings may be related to the higher fermentative capacity of the hindgut of the adult pigs compared to humans (Stevens, 1988). In contrast, FFAR2 and FFAR3 were found expressed in colonic enteroendocrine L-cells responding to increased levels of SCFA (i.e. butyrate) released after high inclusion of resistant starch (Haenen *et al.*, 2013). In addition, a co-expression pattern was uncovered between FFAR2 and FFAR3 with PYY, GLP-1 and serotonin in pig colon (Weatherburn, 2015).

Gene polymorphisms in fatty acid sensing

The ability to sense fats has been associated with an increased consumption of fatty foods, higher BMI and obesity (Stewart *et al.*, 2011; Ichimura *et al.*, 2012). FFA4 gene variants have been found to have a significant impact on receptor responses (Hudson *et al.*, 2013). In addition, the FFAR4 mutation was found to increase the risk of obesity, demonstrating the key role in fat sensing and the control of energy balance in humans and rodents (Ichimura *et al.*, 2012). In addition, FA transporter CD36 was shown to play a crucial role in oral fat sensing as well (Pepino *et al.*, 2012). Genetic CD36 variants were associated with the taste intensity of oleic acid and triolein, total dietary fat and energy intake, and the development of obesity in teenagers (Toguri, 2008; Pepino *et al.*, 2012; Keller *et al.*, 2012; Daoudi *et al.*, 2015; Mrizak *et al.*, 2015). In addition, CD36 gene variants have also been implicated in obesity, type 2 diabetes, the metabolic syndrome, hypertension and coronary heart disease (Precone *et al.*, 2019).

In pigs Da Silva *et al.* (2014) revealed a low incidence of polymorphisms in FFARs genes when comparing to bitter taste sensors. In particular, the total number of SNP for FFAR1, FFAR2, FFAR3, and FFAR4 were 8 (4 ns), 11 (1 ns), 11 (2 ns) and 1 (0 ns), respectively (Da Silva *et al.*, 2014). In addition, the results published from the genomic analysis in pigs by Clop *et al.* (2016) identified three CD36 variants associated with growth and fat deposition. Finally, significant differences in allele frequencies of FFAR4 were observed between two extreme pig groups based on growth rates (Fontanesi *et al.*, 2015).

Bitter sensing

Bitter sensing has been associated with harmful contaminants, toxic compounds and general synthetic chemicals such as pharmaceuticals present in foods/feeds (Nelson and Sanregret, 1997; Meyerhof *et al.*, 2009). These compounds cause defensive and protective responses in the host including food aversion, vomiting, and inhibition of gastric motility and activation of efflux from enterocytes accompanied by an increase in satiation and satiety (Sarkadi *et al.*, 2006; Jeon *et al.*, 2011; Avau *et al.*, 2015; Deloose *et al.*, 2017a and

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2017b). In contrast, some non-toxic plant-derived compounds (such as polyphenols) may also elicit bitter taste (Soares *et al.*, 2018). Overall, close to 1000 compounds are known to be bitter to humans while 81 to laboratory rodents and 27 to pigs (Wang *et al.*, 2017; Roura and Fu, 2017; Dagan-Wiener *et al.*, 2019).

Bitter sensors in the gastrointestinal tract

Bitterants activate the TAS2R family, which consists of 25 functional genes in humans (Meyerhof *et al.*, 2009). The size of the bitter taste receptor (TAS2R) repertoire is species specific, ranging from the 36 genes in the rat to none in carnivorous marine mammals (Roura and Foster, 2018). The sensitivity of pigs to bitterness has been widely reported in the literature (Nelson and Sanregret, 1997; Danilova *et al.*, 1999; Roura *et al.*, 2008; Roura and Navarro, 2018). The porcine pTas2r repertoire was recently characterized consisting of 16 functional genes and 3 pseudogenes (Colombo *et al.*, 2012; Roura, *et al.*, 2016; Roura and Fu, 2017).

Bitter sensing and the enteroendocrine system

TAS2R transcripts have been observed in the oral and GIT mucosa of several mammalian species including humans and pigs (Rozengurt, 2006; Da Silva *et al.*, 2014). In humans, TAS2R5 and TAS2R38 have been co-localized with GLP-1-, CCK- and PYY-labelled EECs in the human small intestine and colon and TAS2R10 with ghrelin cells in the human stomach (Park *et al.*, 2015; Latorre *et al.*, 2016; Wang *et al.*, 2019). Bitter herbal medicines were shown to affect GLP-1 and CCK release in EEC lines (Avau and Depoortere, 2016). However, the active compounds of the medicinal extracts studied remain to be identified. Finally, in tuft cells, bitter agonist denatonium benzoate elicited a paracrine activation of enterocytes presumably following the release of acetylcholine (Schutz *et al.*, 2015).

The presence of pTas2r in the porcine GIT has been reported by several groups (Colombo *et al.*, 2012; Da Silva *et al.*, 2014; Ribani *et al.*, 2017; Clop *et al.*, 2016). However, little is known to date about the function, except that dietary quinine and caffeine increased plasma insulin and GLP-1 (Fu *et al.*, 2018).

Gene polymorphisms in bitter sensing

TAS2R38 variants determine the sensitivity to bitter substance phenylthiocarbamide in humans (Sandell and Breslin, 2006; Risso *et al.*, 2016) and have been associated with food preferences (Sandell and Breslin, 2006), alcohol intake (Duffy *et al.*, 2004), obesity (Tepper *et al.*, 2008) and susceptibility to respiratory pathogens (Lee *et al.*, 2012). Similarly, other gene variants of TAS2R14 and TAS2R50 have been associated with human diseases such as cancer and cardiovascular disease, respectively (Campa *et al.*, 2010; Akao *et al.*, 2012). In addition, TAS2R16 variants appear to have had an evolutionary role to prevent consumption of dangerous raw foods (Valente *et al.*, 2018). Other genetic TAS2Rs have been related to the perception of bitterness in coffee (TAS2R2, TAS2R4 and TAS2R5), alcohol consumption (TAS2R13) and grapefruit liking (TAS2R19) (Hayes *et al.*, 2013).

The porcine bitter taste system presented a high incidence of allelic variants compared with the non-bitter taste genes, suggesting a potential role for these genes in ecological adaptation in pigs (Da Silva *et al.*, 2014). This high variability within and between species of the TAS2R gene repertoire seems to reflect an adaptive nature to survive in specific/novel ecological niches particularly to avoid plant-derived toxins. In addition, three phenotype–genotype studies reported SNPs with functional significance on the porcine bitter receptors pTas2r38, pTas2r39 (Clop *et al.*, 2016; Ribani *et al.*, 2017) and pTas2r40 (Herrero-Medrano *et al.*, 2014). The associations reflected the impact of the fixed alleles on pig growth, fat deposition and environmental adaptation.

Microbial and parasite sensing in the gastrointestinal tract

While the role of nutrient receptors and transceptors has been mostly linked to exogenous or dietary nutrients and potential harmful compounds, recent findings indicate that this sensors may also respond to compounds produced within the intestinal tract. For example, products of the microbial population in the GIT, such as SCFA and MCFA, have the capacity to affect the chemosensory system. Similarly, metabolites produced in the GIT by parasitic or protozoan infections may also be able to activate some of the receptors and transceptors.

Microbial metabolites

SCFA and MCFA resulting from bacterial fermentation in the GIT affect the expression of nutrient sensors and gut peptides in EECs (Steensels and Depoortere, 2018). A decrease in FA sensors (FFAR1, FFAR4 and CD36), together with an increase in glucose and AA sensors (TAS1R3 and SGLT1), were reported in germ-free mice (Duca *et al.*, 2012; Swartz *et al.*, 2012). These changes were associated with reduced CCK, GLP-1 and PYY. In addition, bacterial endotoxins activate the toll-like receptors which are co-localized in CCK, PYY and serotonin secreting EECs (Bogunovic *et al.*, 2007; Larraufie *et al.*, 2017).

Commensal bacteria have evolved to produce metabolites that chemically mimic mammalian agonists and trigger eukaryotic cellular responses (Cohen *et al.*, 2015). Bacterial *N*-acyl amides showed high affinity to host GPR119 functioning to regulate GIT physiology, gut hormones and glucose homeostasis (Cohen *et al.*, 2017). Sung *et al.* (2017) replicated the positive effect of oral resveratrol by fecal microbiome transplants to obese (but naive to dietary resveratrol) mice. In addition, *Clostridium coli* and *Escherichia coli* were shown to affect intestinal motility by modulating serotonin synthesis from enterochromaffin cells (Cao *et al.*, 2017). Taken together, robust evidences are accumulating, showing that gut microbes have evolved to interact and modulate animal host GIT physiology.

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Parasites

Parasitic worms and protozoan infections initiate a signalling cascade in tuft cells mediated by TAS1Rs and/or TAS2Rs (Gerbe *et al.*, 2016; Howitt *et al.*, 2016; von Moltke *et al.*, 2016). Tuft cells orchestrate type 2 cell-mediated immunity in a process where TR sensing signals mediate the differentiation of epithelial crypt progenitors to tuft cells and goblet cells. Tuft and goblet cells hyperplasia is instrumental to achieve worm clearance (Zhao *et al.*, 2008). Furthermore, the succinate receptor and TAS2Rs are expressed on tuft cells to detect the metabolites secreted by the parasites (Nadjsombati *et al.*, 2018; Luo *et al.*, 2019).

Conclusions

The nutrient and non-nutrient sensing in the GIT tract has evolved as a continuum function necessary to orchestrate ingestion, digestion, absorption, metabolism and neutralization of harmful substances. The mechanisms related to the sensing of carbohydrates, AAs, FAs, bitter compounds and microbial and parasite metabolites involve specialized cells in the enteric mucosa (i.e. EEC) that elicit hormonal responses (i.e. CCK, GLP-1, PYY, ghrelin, etc.) which, in turn, mediate changes in passage rate and appetite. Gene variations have been related to food choices in humans while in pigs to ecological adaptations particularly regarding the bitter taste receptor repertoire. In addition, genetic mutations have the potential to lead to the development of novel nutritional strategies in pigs, for example, regarding FFA sensing. In addition, our understanding on the impact of gut microbiome on the host's gut-brain communications has started to unfold.

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Declaration of interest

The authors declare no conflicts of interest.

Ethics statement

Not applicable.

Software and data repository resources

Not applicable.

Supplementary material

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References

Aji GK, Warren FJ and Roura E 2019. Starch, salivary α-amylase activity and maltose taste thresholds in humans. Chemical Senses 44, 249–256.

Akao H, Polisecki E, Kajinami K, Trompet S, Robertson M, Ford I, Jukema JW, de Craen AJ, Westendorp RG, Shepherd J, Packard C, Buckley BM and Schaefer EJ 2012. KIF6, LPA, TAS2R50, and VAMP8 genetic variation, low density lipoprotein cholesterol lowering response to pravastatin, and heart disease risk reduction in the elderly. Atherosclerosis 220, 456–462.

Avau B and Depoortere I 2016. The bitter truth about bitter taste receptors: beyond sensing bitter in the oral cavity. Acta Physiologica 216, 407–420.

Avau B, Rotondo A, Thijs T, Andrews CN, Janssen P, Tack J and Depoortere I 2015. Targetin extra-oral bitter taste receptors modulates gastrointestinal motility with effects on satiation. Scientific Reports 5, 15985. doi: 10.1038/srep15985.

Bachmanov AA and Beauchamp GK 2007. Taste receptor genes. Annual Review of Nutrition 27, 389–414.

Badman MK and Flier JS 2005. The gut and energy balance: visceral allies in the obesity wars. Science 307, 1909–1914.

Barretto RPJ, Gillis-Smith S, Chandrashekar J, Yarmolinsky, DA, Schnitzer MJ, Ryba NJP and Zuker CS 2015. The neural representation of taste quality at the periphery. Nature 517, 373–376.

Berridge KC and Robinson TE 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Research Reviews 28, 309–369.

Bogunovic M, Dave SH, Tilstra JS, Chang DT, Harpaz N, Xiong H, Mayer LF and Plevy SE 2007. Enteroendocrine cells express functional toll-like receptors. American Journal of Physiology. Gastrointestinal and Liver Physiology 292, 1770–1783.

Broer S 2008. Amino acid transport across mammalian renal and intestinal epithelia. Physiological Reviews 88, 249–286.

Campa D, Vodicka P, Pardini B, Naccarati A, Carrai M, Vodickova L, Novotny J, Hemminki K, Försti A, Barale R and Canzian F 2010. A gene-wide investigation on polymorphisms in the taste receptor 2R14 (TAS2R14) and susceptibility to colorectal cancer. BioMed Central Medical Genetics 11, 88. doi: 10.1186/1471-2350-11-88.

Canfora EE, Jocken JW and Blaak EE 2015. Short-chain fatty acids in control of body weight and insulin sensitivity. Natural Reviews Endocrinology 11, 577–591.

Cao H, Liu X, An Y, Zhou G, Liu Y, Xu M, Dong W, Wang S, Yan F, Jiang K and Wang B 2017. Dysbiosis contributes to chronic constipation development via regulation of serotonin transporter in the intestine. Scientific Reports 7, 10322. doi: 10.1038/s41598-017-10835-8.

Chen QY, Alarcon S, Tharp A, Ahmed OM, Estrella NL, Greene TA, Rucker J and Breslin PA 2009. Perceptual variation in umami taste and polymorphisms in TAS1R taste receptor genes. American Journal of Clinical Nutrition 90, 770–779.

Cheng MW, Chegeni M, Kim KH, Zhang G, Benmoussa M, Quezada-Calvillo R, Nichols BL and Hamaker BR 2014. Different sucrose-isomaltase response of Caco-2 cells to glucose and maltose suggests dietary maltose sensing. Journal of Clinical Biochemistry and Nutrition 54, 55–60.

Choi S, Lee M, Shiu AL, Yo SJ, Halldén G and Aponte GW 2007. GPR93 activation by protein hydrolysate induces CCK transcription and secretion in STC-1 cells. American Journal of Physiology. Gastrointestinal and Liver Physiology 292, 1366–1375.

Clop A, Sharaf A, Castello A, Ramos-Onsins S, Cirera S, Mercade A, Derdak S, Huisman A, Fredholm M, van As P and Sanchez A 2016. Identification of protein-damaging mutations in 10 swine taste receptors and 191 appetite-reward genes. BioMed Central Genomics 17, 685. doi: 10.1186/s12864-016-2972-z.

Cohen LJ, Esterhazy D, Kim S-H, Lemetre C, Aguilar RR, Gordon EA, Pickard AJ, Cross JR, Emiliano AB, Han SM, Chu J, Vila-Farres X, Kaplitt J, Rogoz A, Calle PY, Hunter C, Bitok JK and Brady SF 2017. Commensal bacteria make GPCR ligands that mimic human signalling molecules. Nature 549, 48–53.

Cohen LJ, Kang H-S, Chu J, Huang Y-H, Gordon EA, Reddy BVB, Ternei MA, Craig JW and Brady SF 2015. Functional metagenomic discovery of bacterial effectors in the human microbiome and isolation of commendamide, a GPCR G2A/132 agonist. Proceedings of the National Academy of Sciences of the United States of America 112, 4825–4834.

Colombo M, Trevisi P, Gandolfi G and Bosi P 2012. Assessment of the presence of chemosensing receptors based on bitter and fat taste in the gastrointestinal tract of young pig. Journal of Animal Science 90, 128–130.

Dagan-Wiener A, Di Pizio A, Nissim I, Bahia MS, Dubovski N, Margulis E and Masha Y 2019. BitterDB: taste ligands and receptors database in 2019. Nucleic Acids Research 47, 1179–1185.

Daniel H and Zietek T 2015. Taste and move: glucose and peptide transporters in the gastrointestinal tract. Experimental Physiology 100, 1441–1450.

Danilova V, Roberts T and Hellekant G 1999. Responses of single taste fibers and whole chorda tympani and glossopharyngeal nerve in the domestic pig, *Sus scrofa*. Chemical Senses 24, 301–316.

Daoudi H, Plesník J, Sayed A, Šerý O, Rouabah A, Rouabah L and Khan NA 2015. Oral fat sensing and CD36 gene polymorphism in Algerian lean and obese teenagers. Nutrients 7, 9096–9104.

Da Silva, EC, De Jager N, Burgos W, Reverter A, Perez-Enciso M and Roura E 2014. Characterization of the porcine GPCR nutrient sensor and taste receptor gene repertoire across international and local domestic breeds and wild populations. BioMed Central Genomics 15, 1057.

Dehmlow H, Alvarez Sanchez R, Bachmann S, Bissantz, C, Bliss F, Conde-Knape K, Graf M, Martin RE, Obst Sander U, Raab S, Richter HGF, Sewing S, Sprecher U, Ullmer C and Mattei P 2013. Discovery and optimisation of 1-hydroxyimino-3,3-diphenylpropane, a new class of orally active GPBAR1 (TGR5) agonists. Bioorganic & Medical Chemistry Letters 23, 4627–4632.

De Jager N, Zhan M, Rzepus M and Roura E 2013. Towards defining the taste receptor repertoire in the pig. In Proceedings of Manipulating Pig Production XIV, APSA Conference, 24–27 November 2013, Melbourne, Australia, pp. 47.

Deloose E, Corsetti M, Van Oudenhove L, Depoortere I and Tack J 2017a. Intragastric infusion of the bitter tastan quinine suppresses hormone release and antral motility during the fastin state in health female volunteers. Neurogastroenterology and Motility 30, 313171. doi: 10.1111/nmo.13171.

Deloose E, Janssen P, Corsetti M, Biesiejiersji J, Masuy I, Rotondo A, Van Oudenhove L, Depoortere I and Tack J 2017b. Intragastric infusion of denatonium benzoate attenuates interdigestive gastric motility and hunger scores in healthy female volunteers. The American Journal of Clinical Nutrition 105, 580–588.

Depoortere I 2014. Taste receptors of the gut: emerging roles in health and disease. Gut 63, 179–190.

Diakogiannaki E, Pais R, Tolhurst G, Parker HE, Horscroft J, Horscroft J, Rauscher B, Zietek T, Daniel H, Gribble FM and Reinmann F 2013. Oligopeptides stimulate glucagon-like peptide-1 secretion in mice through proton-coupled uptake and the calcium-sensing re-ceptor. Diabetologia 56, 2688–2696.

Diallinas G 2017. Transceptors as a functional link of transporters and receptors. Microbial cell 4, 69–73.

Dias AG, Eny KM, Cockburn M, Chiu W, Nielsen DE, Duizer L and El-Sohemy A 2015. Variation in the TAS1R2 gene, sweet taste perception and intake of sugars. Journal of Nutrigenetics and Nutrigenomics 8, 81–90.

Douard V and Ferraris RP 2008. Regulation of the fructose transporter GLUT5 in health and disease. American Journal of Physiology, Endocrinology and Metabolism 295, 227–237.

Duca FA, Swartz TD, Sakar Y and Covasa M 2012. Increased oral detection, but decreased intestinal signaling for fats in mice lacking gut microbiota. PLoS ONE 7, e39748. doi: 10.1371/journal.pone.0039748.

Duffy VB, Davidson AC, Kidd JR, Kidd KK, Speed WC, Pakstis AJ, Reed DR, Snyder DJ and Bartoshuk LM 2004. Bitter receptor gene (TAS2R38), 6-n-propylthiouracil (PROP) bitterness and alcohol intake. Alcoholism Clinical and Experimental Research 28, 1629–1637.

Engelstoft MS, Park WM, Sakata I, Kristensen LV, Husted AS, Osborne-Lawrence S, Piper PK, Walker AK, Pedersen MH, Nøhr MK, Pan J, Sinz CJ, Carrington PE, Akiyama TE, Jones RM, Tang C, Ahmed K, Offermanns S, Egerod KL, Zigman JM and Schwartz TW 2013. Seven transmembrane G protein-coupled receptor repertoire of gastric ghrelin cells. Molecular Metabolism 2, 376–392.

Eny KM, Wolever TM, Corey PN and El-Sohemy A 2010. Genetic variation in TAS1R2 (Ile191Val) is associated with consumption of sugars in overweight and obese individuals in 2 distinct populations. American Journal of Clinical Nutrition 92, 1501–1510.

Fleischer J, Bumbalo R, Bautze V, Strotmann J and Breer H 2015. Expression of odorant receptor Olfr78 in enteroendocrine cells of the colon. Cell Tissue Research 361, 697–710.

Fontanesi L, Bertolini F, Scotti E, Schiavo G, Colombo M, Trevisi P, Riban A, Buttazzoni A,Russo V and Dall'Olio S 2015. Next Generation Semiconductor based-sequencing of a nutrigenetics target gene (GPR120) and association with growth rate in Italian large white pigs. Animal Biotechnology 26, 92–97.

Fu M, Val-Laillet D, Guerin S and Roura E 2018. Dietary bitter compounds delayed gastric emptying and glucose uptake while increased plasma insulinotropic hormone GLP-1 in pigs. In Proceedings of the 14th International Symposium of Digestive Physiology of Pigs, 21–24 August 2018, Brisbane, Australia, pp. 207.

Gerbe F, Sidot E, Smyth DJ, Ohmoto M, Matsumoto I, Dardalhon V, Cesses P, Garnier L, Pouzolles M, Brulin B, Bruschi M, Harcus Y, Zimmermann V, Taylor N, Maizels RM and Jay P 2016. Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. Nature 529, 226–30.

Gerspach AC, Steinert RE, Schonenberger L, Graber-Maier A and Beglinger C 2011. The role of the gut sweet taste receptor in regulating GLP-1, PYY, and CCK release in humans. American Journal of Physiology Endocrinology and Metabolism 301, 317–325.

Glaser D, Wanner M, Tinti JM and Nofre C 2000. Gustatory responses of pigs to various natural and artificial compounds known to be sweet in man. Food Chemistry 68, 375–385.

Glendinning JI, Stano S, Holter M, Azenkot T, Goldman O, Margolskee RF, Vasselli JR and Sclafani A 2015. Sugar-induced cephalic-phase insulin release is mediated by a T1r2+T1r3-independent taste transduction pathway in mice. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 309, 552–560.

Haenen D, Zhang J, Souza da Silva C, Bosch G, van der Meer IM, van Arkel J, van den Borne JJ, Perez Gutierrez O, Smidt H, Kemp B, Muller M and Hooiveld GJ 2013. A diet high in resistant starch modulates microbiota composition, SCFA concentrations, and gene expression in pig intestine. Journal of Nutrition 143, 274–283.

Haid DC, Jordan-Biegger C, Widmayer P and Breer H 2012. Receptors responsive to protein breakdown products in G-cells and D-cells of mouse, swine and human. Frontiers in Physiology 3, 65. doi: 10.3389/fphys.2012.00065.

Han P, Keast R and Roura E 2017. Salivary leptin and TAS1R2/TAS1R3 polymorphisms are related to sweet taste sensitivity and carbohydrate intake in a buffet meal. British Journal of Nutrition 118, 763–770.

Han P, Keast R and Roura E 2018. TAS1R1 and TAS1R3 polymorphic genotypes relate to savoury and protein-rich food choices from a buffet meal in young adults. Nutrients 10, 1906. doi: 10.3390/nu10121906.

Hansen HS, Rosenkilde MM, Holst JJ and Schwartz TW 2012. GPR119 as a fat sensor. Trends in Pharmacological Sciences 33, 374–381.

Hara T, Kashihara D, Ichimura A, Kimura I, Tsujimoto G and Hirasawa A 2014. Role of free fatty acid receptors in the regulation of energy metabolism. Biochimica et Biophysica Acta 1841, 1292–1300.

Hayes JE, Feeney EL and Alle AL 2013. Do polymorphisms in chemosensory genes matter for human ingestive behavior? Food Quality and Preference 30, 202–216.

Herrero-Medrano JM, Megens HJ, Groenen MAM, Bose M, Pérez-Enciso M and Crooijmans RPMA 2014. Whole-genome sequence analysis reveals differences in population management and selection of European low-input pig breeds. BioMed Central Genomics 15, 601. doi: 10.1186/1471-2164-15-601.

Howitt MR, Lavoie S, Michaud M, Blum AM, Tran SV, Weinstock JV, Gallini CA, Redding K, Margolskee RF, Osborne LC, Artis D and Garrett WS 2016. Tuft cells, taste-chemosensory cells, orchestrate parasite type 2 immunity in the gut. Science 351, 1329–1333.

Hudson BD, Murdoch H and Milligan G 2013. Minireview: the effects of species ortholog and SNP variation on receptors for free fatty acids. Molecular Endocrinology 27, 1177–1187.

Humphrey B, Tedó G, Klasing KC and Roura E 2009. Caractérisation des polypeptides récepteurs umami porcins (pT1r1 et pT1r3). Journées de la Recherche Porcine 41, 165–166.

Ichimura A, Hirasawa A, Poulain-Godefroy O, Bonnefond A, Hara T, Yengo L, Kimura I, Leloire A, Liu N, Iida K, Choquet H, Besnard P, Lecoeur C, Vivequin S, Ayukawa K, Takeuchi M, Ozawa K, Tauber M, Maffeis C, Morandi A, Buzzetti R, Elliott P, Pouta A, Jarvelin MR, Körner A, Kiess W, Pigeyre M, Caiazzo R, Van Hul W, Van Gaal L, Horber F, Balkau B, Lévy-Marchal C, Rouskas K, Kouvatsi A, Hebebrand J, Hinney A, Scherag A, Pattou F, Meyre D, Koshimizu TA, Wolowczuk I, Tsujimoto G and Froguel P 2012. Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human. Nature 483, 350–354.

Ikeda K 1909. New seasonings. Journal of Tokyo Chemical Society 30, 820–836.

Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, Kim HH, Xu X, Chan SL, Juhaszova M, Bernier M, Mosinger B, Margolskee RF and Egan JM 2007. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proceedings of the National Academy of Sciences of the United States of America* 104, 15069–15074.

Janssen S, Laermans J, Iwakura H, Tack J and Depoortere I 2012. Sensing of fatty acids for octanoylation of ghrelin involves a gustatory G-protein. PLoS ONE 7, e40168. doi: 10.1371/journal.pone.0040168.

https://doi.org/10.1017/S1751731119001794 Published online by Cambridge University Press

Jeon T-I, Seo YK and Osborne TF 2011. Gut bitter taste receptor signalling induces ABCB1 through a mechanism involving CCK. Biochemical Journal 438, 33–37.

Keller KL, Liang LCH, Sakimura J, May D, van Belle C, Breen C, Driggin E, Tepper BJ, Lanzano PC, Deng L and Chung WK 2012. Common variants in the CD36 gene are associated with oral fat perception, fat preferences, and obesity in African Americans. Obesity (Silver Spring) 20, 1066–1073.

Kim UK, Wooding S, Riaz N, Jorde LB and Drayna D 2006. Variation in the human TAS1R taste receptor genes. Chemical Senses 31, 599–611.

Lan H, Vassileva G, Corona A, Liu L, Baker H, Golovko A, Abbondanzo SJ, Hu W, Yang S, Ning Y, Del Vecchio RA, Poulet F, Laverty M, Gustafson EL, Hedrick JA and Kowalski TJ 2009. GPR119 is required for physiological regulation of glucagon-like peptide-1 secretion but not for metabolic homeostasis. Journal of Endocrinology 201, 219–230.

Lapis TJ, Penner MH and Lim J 2014. Evidence that humans can taste glucose polymers. Chemical Senses 39, 737–747.

Larraufie P, Dore J, Lapaque N and Blottiere HM 2017. TLR ligands and butyrate increase Pyy expression through two distinct but inter-regulated pathways. Cellular Microbiology 19, e12648. doi: 10.1111/cmi.12648.

Latorre R, Huynh J, Mazzoni M, Gupta A, Bonora E, Clavenzani P, Chang L, Mayer EA, De Giorgio R and Sternini C 2016. Expression of the bitter taste receptor, T2R38, in enteroendocrine cells of the colonic mucosa of overweight/obese vs. lean subjects. PLoS ONE 11, e0147468. doi: 10.1371/journal.pone.0147468.

Lee RJ, Xiong G, Kofonow JM, Chen B, Lysenko A, Jiang P, Abraham V, Doghramji L, Adappa ND, Palmer JN, Kennedy DW, Beauchamp GK, Doulias PT, Ischiropoulos H, Kreindler JL, Reed DR and Cohen NA 2012. T2R38 taste receptor polymorphisms underlie susceptibility to upper respiratory infection. The Journal of Clinical Investigation 122, 4145–4159.

Lin HV, Frassetto A, Kowalik EJ Jr., Nawrocki AR, Lu MM, Kosinski JR, Hubert JA, Szeto D, Yao X, Forrest G and Marsh DJ 2012. Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. PLoS ONE 7, e35240. doi: 10.1371/journal.pone.0035240.

Liou AP, Sei Y, Zhao X, Feng J, Lu X, Thomas C, Raybould HE and Wank SA 2011a. The extracellular calcium-sensing receptor is required for cholecystokinin secretion in response to L-phenylalanine in acutely isolated intestinal I cells. American Journal of Physiology Gastrointestinal and Liver Physiology 300, 538–546.

Liu D, Costanzo A, Evans MDM, Archer NS, Nowson C, Duesing K and Keast R 2018. Expression of the candidate fat taste receptors in human fungiform papillae and the association with fat taste function. British Journal of Nutrition 120, 64–73.

Low JY, Lacy KE, McBride RL and Keast RSJ 2017. Carbohydrate taste sensitivity is associated with starch intake and waist circumference in adults. Journal of Nutrition 147, 2235–2242.

Luo XC, Chen ZH, Xue JB, Zhao DX, Lu C, Li YH, Li SM, Du YW, Liu Q, Wang P, Liu M and Huang L 2019. Infection by the parasitic helminth Trichinella spiralis activates a Tas2r-mediated signaling pathway in intestinal tuft cells. Proceedings of the National Academy of Sciences of the United States of America 116, 5564–5569.

Mace OJ, Affleck J, Patel N and Kellett GL 2007. Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. The Journal of Physiology 582, 379–392.

Margolskee RF, Dyer J, Kokrashvili Z, Salmon KSH, Ilegems E, Daly K, Maillet EL, Ninomiya Y, Mosinger B and Shirazi-Beechey SP 2007. T1R3 and gustducin in gut sense sugars to regulate exression of Na+-glucose cotransporter 1. Proceedings of the National Academy of Sciences of the United States of America 104, 15075–15080.

Mattes RD 2011. Accumulating evidence supports a taste component for free fatty acids in humans. Physiology and Behavior 104, 624–631.

Meyerhof W, Batram C, Kuhn C, Brockhoff A, Chudoba E, Bufe B, Appendino G and Behrens M 2009. The molecular receptive ranges of human TAS2R bitter taste receptors. Chemical senses 35, 157–170.

Modvig IM, Kuhre RE and Holst JJ 2019. Peptone-mediated glucagon-like peptide-1 secretion depends on intestinal absorption and activation of basolaterally located calcium-sensing receptors. Physiological Reports 7, e14056. doi: 10.14814/phy2.14056.

Moran AW, Al-Rammahi MA, Arora DK, Batchelor DJ, Coulter EA, Daly K, Ionescu C, Bravo D, and Shirazi-Beechey SP 2010a. Expression of Na+/glucose co-transporter 1 (SGLT1) is enhanced by supplementation of the diet of weaning piglets with artificial sweeteners. British Journal of Nutrition 104, 637–646.

Moran AW, Al-Rammahi MA, Arora DK, Batchelor DJ, Coulter EA, Ionescu C, Bravo D and Shirazi-Beechey SP, 2010b. Expression of Na+/glucose co-transporter 1 (SGLT1) in the intestine of piglets weaned to different concentrations of dietary carbohydrate. British Journal of Nutrition 104, 647–655.

Morrison DJ and Preston T 2016. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes 7, 189–200.

Moss CE, Glass LL, Diakogiannaki E, Pais R, Lenaghan C, Smith DM, Wedin M, Bohlooly-Y M, Gribble FM and Reimann F 2016. Lipid derivatives activate GPR119 and trigger GLP-1 secretion in primary murine L-cells. Peptides 77, 16–20.

Mrizak I, Sery O, Plesnik J, Arfa A, Fekih M, Bouslema A, Zaouali M, Tabka Z and Khan NA 2015. The A allele of cluster of differentiation 36 (CD36) SNP 1761667 associates with decreased lipid taste perception in obese Tunisian women. British Journal of Nutrition 113, 1330–1337.

Nadjsombati MS, McGinty JW, Lyons-Cohen MR, Jaffe JB, DiPeso L, Schneider C, Miller CN, Pollack JL, Nagana Gowda GA, Fontana MF, Erle DJ, Anderson MS, Locksley RM, Raftery D and von Moltke J 2018. Detection of succinate by intestinal tuft cells triggers a type 2 innate immune circuit. Immunity 49, 33–41.

Nelson G, Chandrashekar J, Hoon MA, Feng LX, Zhao G, Ryba NJ and Zuker CS 2002. An amino-acid taste receptor. Nature 416, 199–202.

Nelson SL and Sanregret JD 1997. Response of pigs to bitter-tasting compounds. Chemical Senses 22, 129–132.

Nøhr MK, Pedersen MH, Gille A, Egerod KL, Engelstoft MS, Husted AS, Sichlau RM, Grundda KVl, Poulsen SS, Han S, Jones RM, Offermanns S and Schwartz TW 2013. GPR41/FFAR3 and GPR43/FFAR2 as cosensors for short-chain fatty acids in enteroendocrine cells vs FFAR3 in enteric neurons and FFAR2 in enteric leukocytes. Endocrinology 154, 3552–3564.

Overton HA, Fyfe MCT and Reynet C 2008. GPR119, a novel G protein-coupled receptor target for the treatment of type 2 diabetes and obesity. British Journal of Pharmacology 153, 76–81.

Park J, Kim KS, Kim KH, Lee IS, Jeong HS, Kim Y and Jang HJ 2015. GLP-1 secretion is stimulated by 1,10-phenanthroline via colocalized T2R5 signal transduction in human enteroendocrine L cell. Biochemical and Biophysical Research Communications 468, 306–311.

Pepino MY, Love-Gregory L, Klein S and Abumrad NA 2012. The fatty acid translocase gene CD36 and lingual lipase influence oral sensitivity to fat in obese subjects. The Journal of Lipid Research 53, 561–566.

Pluznick J 2014. A novel SCFA receptor, the microbiota, and blood pressure regulation. Gut Microbes 5, 202–207.

Poncet N and Taylor PM 2013. The role of amino acid transporters in nutrition. Current Opinion in Clinical Nutrition and Metabolic Care 16, 57–65.

Poreba MA, Dong CX, Li SK, Stahl A, Miner JH and Brubaker PL 2012. Role of fatty acid transport protein 4 in oleic acid-induced glucagon-like peptide-1 secretion from murine intestinal L cells. American Journal of Physiology Endocrinology and Metabolism 303, 899–907.

Precone V, Beccari T, Stuppia I, Baglivo M, Paolacci S, Manara E, Miggiano GAD, Falsini B, Trifirò A, Zanlari A, Herbst KL, Unfer V and Bertelli M 2019. Taste, olfactory and texture related genes and food choices: implications on health status. European Review for Medical and Pharmacological Sciences 23, 1305–1321.

Raliou M, Wiencis A, Pillias AM, Planchais A, Eloit C, Boucher Y, Trotier D, Montmayeur JP and Faurion A 2009. Nonsynonymous single nucleotide polymorphisms in human tas1r1, tas1r3, and mGluR1 and individual taste sensitivity to glutamate. American Journal of Clinical Nutrition 90, 789–799.

Ramos-Lopez O, Panduro A, Martinez-Lopez E and Roman S 2016. Sweet taste receptor TAS1R2 poly-morphism (Val191Val) is associated with a higher carbohydrate intake and hypertriglyceridemia among the population of West Mexico. Nutrients 8, 101.

Reimann F, Habib AM, Tolhurst G, Parker HE, Rogers GJ and Gribble FM 2008. Glucose sensing in L cells: a primary cell study. Cell Metabolism 8:532–539.

Reimann F, Ward PS and Gribble FM 2006. Signaling mechanisms underlying the release of glucagon-like peptide 1. Diabetes 55, 78–85.

Rettenberger AT, Schulze W, Breer H and Haid D 2015. Analysis of th eprotein related receptor GPR92 in G-cells. Frontiers in Physiology 6, 261. doi: 10.3389/fphys.2015.00261.

https://doi.org/10.1017/S1751731119001794 Published online by Cambridge University Press

Ribani A, Bertolini F, Schiavo G, Scotti E, Utzeri VJ, Dall'Olio S, Trevisi P, Bosi P and Fontanesi L 2017. Next generation semiconductor based sequencing of bitter taste receptor genes in different pig populations and association analysis using a selective DNA pool-seq approach. Animal Genetics 48, 97–102.

Risso DS, Mezzavilla M, Pagani L, Robino A, Morini G, Tofanelli S, Carrai M, Campa D, Barale R, Caradonna F, Gasparini P, Luiselli D, Wooding S and Drayna D 2016. Global diversity in the TAS2R38 bitter taste receptor: revisiting a classic evolutionary proposal. Scientific Reports 6, 25506. doi: 10.1038/srep25506.

Roura E and Foster S 2018. Nutrient-sensing biology in mammals and birds. Annual Reviews Animal Biosciences 6, 197–225.

Roura E and Fu M 2017. Taste receptors and feed intake in pigs (130 years of research: then, now and future). Animal Feed Science and Technology 233, 3–12.

Roura E, Humphrey B, Klasing KC and Swart M 2011. Is the pig a good umami sensing model for humans? A comparative taste receptor study. Flavour and Fragrance Journal 26, 282–285.

Roura E, Humphrey B, Tedó G and Ipharragerre I 2008. Unfolding the codes of short-term feed appetence in farm and companion animals. A comparative oronasal nutrient sensing biology review. Canadian Journal of Animal Science 88, 535–558.

Roura E, Koopmans SJ, Lallès JP, Le Huerou-Luron I, de Jager N, Schuurman T and Val-Laillet D 2016. Critical review evaluating the pig as a model for human nutritional physiology. Nutrition Research Reviews 29, 60–90.

Roura E and Navarro M 2018. Physiological and metabolic control of diet selection. Festschrift for Prof John L Black: celebrating 45 years of excellence in animal production science and application. Animal Production Science 58, 613–626.

Roura E, Shrestha B and Diffey S 2013. Pigs show no sensory-motivated intake for several cereal and tuber starches except hydrolysed corn starch. In Proceedings of Manipulating Pig Production XIV, APSA Conference, 24–27 November 2013, Melbourne, Australia, pp. 45.

Rozengurt E 2006. Taste receptors in the gastrointestinal tract. I. Bitter taste receptors and α-gustducin in the mammalian gut. American Journal of Physiology Gastrointestinal and Liver Physiology 291, 171–177.

Rozengurt N, Wu SV, Chen MC, Huang C, Sternini C and Rozengurt E 2006. Colocalization of the alpha-subunit of gustducin with PYY and GLP-1 in L cells of human colon. American Journal of Physiology, Gastrointestinal and Liver Physiology 291, 792–802.

Sandell MA and Breslin PAS 2006. Variability in a taste-receptor gene determines whether we taste toxins in food. Current Biology 16, 792–794.

San Gabriel A and Uneyama H 2013. AA sensing in the gastrointestinal tract. Amino Acids 45, 451–461.

Sarkadi B, Homolya L, Szakacs G and Varadi A 2006. Human multidrug resistance ABCB and ABCG transporters: participation in a chemoimmunity defense system. Physiological Reviews 86, 1179–1236.

Schutz B, Jurastow I, Bader S, Ringer C, von Engelhardt J, Chubanov V, Gudermann T, Diener M, Kunner W, Krasteva-Christ G and Weihe E 2015. Chemical coding and chemosensory properties of cholinergic brush cells in the mouse gastrointestinal and biliary tract. Frontiers in Physiology 6, 87. doi: 10.3389/fphys.2015.00087.

Sclafani A 1987. Carbohydrate taste, appetite, and obesity: an overview. Neuroscience and Biobehavioral Reviews 11, 131–153.

Soares S, Silva, MS, Garcia-Estevez I, GroBmann P, Bras N, Brandao E, Mateus N, de Freitas V, Behrens M and Meyerfof W 2018. Human bitter taste receptors are activated by different classes of polyphenols. Journal of Agricultural and Food Chemistry 66, 8814–8823.

Steensels S, Cools L, Avau B, Vancleef L, Farre R, Verbeke K and Depoortere I 2016. Supplementation of oligofructose, but not sucralose, decreases high-fat diet induced body weight gain in mice independent of gustducin-mediated gut hormone release. Molecular Nutrition and Food Research 61, 1600716. doi: 10.1002/mnfr.201600716

Steensels S and Depoortere I 2018. Chemoreceptors in the gut. Annual Review of Physiology 80, 117–141.

Steinert RE, Gerspach AC, Gutmann H, Asarian L, Drewe J and Beglinger C 2011a. The functional involvement of gut-expressed sweet taste receptors in glucose-stimulated secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). Clinical Nutrition 30, 524–532.

Steinert RE, Frey F, Topfer A, Drewe J and Beglinger C 2011b. Effects of carbohydrate sugars and artificial sweeteners on appetite and the secretion of gastrointestinal satiety peptides. British Journal of Nutrition 105, 1320–1328.

Stevens C.E 1988. Comparative physiology of the vertebrate digestive system. Cambridge University Press, Cambridge, NY, USA.

Stewart JE, Newman LP and Keast RSJ 2011. Oral sensitivity to oleic acid is associated with fat intake and body mass index. Clinical Nutrition 30, 838–844.

Sukumaran SK, Yee KK, Iwata S, Kotha R, Quezada-Calvillo R, Nichols BL, Mohan S, Pinto BM, Shigemura N and Ninomiya Y 2016. Taste cell-expressed α-glucosidase enzymes contribute to gustatory responses to disaccharides. Proceedings of National Academy of Science 113, 6035–6040.

Sundaresan S, Shahid R, Riehl TE, Chandra R, Nassir F, Stenson WF, Liddle RA and Abumrad NA 2013. CD36-dependent signaling mediates fatty acid-induced gut release of secretin and cholecystokinin. The Federation of American Societies for Experimental Biology Journal 27, 1191–1202.

Sung MM, Kim TT, Denou E, Soltys CM, Hamza SM, Byme NJ, Masson G, Park H, Wishart DS, Madsen KL, Shertzer JD and Dyck JR 2017. Improved glucose homeostasis in obese mice treated with resveratrol is associated with alterations in the gut microbiome. Diabetes 66, 418–425.

Swartz TD, Duca FA, de Wouters T, Sakar Y and Covasa M 2012. Up-regulation of intestinal type 1 taste receptor 3 and sodium glucose luminal transporter-1 expression and increased sucrose intake in mice lacking gut microbiota. British Journal of Nutrition 107, 621–630.

Tedo Perez MG 2009. The umami taste in pigs: L-amino acid preferences and in vitro recognition by the receptor dimer pT1r1/pT1r3 expressed in porcine taster and non-taste tissues. PhD Thesis, The Autonomous University of Barcelona, Barcelona, Spain.

Tepper BJ, Koelliker Y, Zhao L, Ullrich NV, Lanzara C, D'Adam P, Ferrara A, Ulivi S, Esposito L and Gasparini P 2008. Variation in the bitter-taste receptor gene TAS2R38, and adiposity in a genetically isolated population in Southern Italy. Obesity 16, 2289–2295.

Tinti JM, Glaser D, Wanner M and Nofre C 2000. Comparison of gustatory responses to AA s in pigs and in humans. Lebensmittel-Wissenschaft and Technologie 33, 578–583.

Toguri C 2008. Genetic Variation in CD36 and Dietary Fat Intake. M.Sc. Dissertation, University of Toronto, Toronto, Canada.

Valente C, Alvarez L, Marques PI, Gusmão L, Amorim A, Seixas S and Prata MJ 2018. Genes from the TAS1R and TAS2R families of taste receptors: looking for signatures of their adaptive role in human evolution. Genome Biology and Evolution 10, 1139–1115.

Vancleef L, Van Den Broeck T, Thijs T, Steensels S, Briand L, Tack J and Depoortere I 2015. Chemosensory signalling pathways involved in sensing of AA s by the ghrelin cell. Scientific Reports 5, 15725. doi: 10.1038/srep15725.

van der Wielen N, van Avesaat M, de Wit NJ, Vogels JT, Troost F, Masclee A, Koopmans SJ, van der Meulen J, Boekschoten MV, Muller M, Hendriks HF, Witkamp RF and Meijerink J 2014. Cross-species comparison of genes related to nutrient sensing mechanisms expressed along the intestine. PLoS ONE 9, e107531. doi: 10.1371/journal.pone.0107531.

Vigors S, Sweeney T, O'Shea CJ, Browne JA, and O'Doherty JV 2014. Improvements in growth performance, bone mineral status and nutrient digestibility in pigs following the dietary inclusion of phytase are accompanied by modifications in intestinal nutrient transporter gene expression. British Journal of Nutrition 112, 688–697.

von Moltke J, Ji M, Liang HE and Locksley RM 2016. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. Nature 529, 221–225.

Wang J, Fu M, Navarro M and Roura E 2017. A double-choice model to quantify negative preference to bitterness in pigs. Animal Production Science 57, 2422–2422.

Wang J, Wu X, Simonavicius N, Tian H and Ling L 2006. Medium-chain fatty acids as ligands for orphan G protein-coupled receptor GPR84. The Journal of Biological Chemistry 281, 34457–34464.

Wang Q, Liszt KI, Deloose E, Canovai E, Thijs T, Farre R, Ceulemans LJ, Lannoo M, Tack J and Depoortere I 2019. Obesity alters adrenergic and chemosensory signaling pathways that regulate ghrelin secretion in the human gut. The FASEB Journal 33, 4907–4920.

Weatherburn DH 2015. Role of short chain fatty acid receptors in the gastrointestinal tract and their potential involvement in appetite control. PhD Thesis, University of Liverpool, Liverpool, Great Britain.

https://doi.org/10.1017/S1751731119001794 Published online by Cambridge University Press

Wellendorph P, Johansen LD and Brauner-Osborne H 2010. Molecular pharmacology of promiscuous seven transmembrane receptors sensing organic nutrients. Molecular Pharmacology 76, 453–465.

Widmayer P, Kusumakshi S, Hägele FA, Boehm U and Breer H 2017. Expression of the fatty acid receptors GPR84 and GPR120 and cytodifferentiation of epithelial cells in the gastric mucosa of mouse pups in the course of dietary transition. Frontiers in Physiology 8, 601. doi: 10.3389/fphys.2017.00601

Young SH, Rey O, Sternini C and Rozengurt E 2010. Amino acid sensing by enteroendocrine STC-1 cells: role of the Na+-coupled neutral amino acid transporter 2. American Journal of Physiology. Cell Physiology 298, 1401–1413.

Zhang C, Huang Y, Jiang Y, Mulpuri N, Wei L, Hamelberg D, Brown EM and Yang JJ 2014. Identification of an l-phenylalanine binding site enhancing the cooperative responses of the calcium-sensing receptor to calcium. Journal of Biological Chemistry 289, 5296–5309.

Zhang G, Hasek LY, Lee BH and Hamaker BR 2015. Gut feedback mechanisms and food intake: a physiological approach to slow carbohydrate bioavailability. Food and Function 6, 1072–1089.

Zhao A, Urban JF, Anthony RM, Sun R, Stiltz J, van Rooijen N, Wynn TA, Gause WC, Shea-Donohue T 2008. Th2 cytokine-induced alterations in intestinal smooth muscle function depend on alternatively activated macrophages. Gastroenterology 135, 217–25.e1. doi: 10.1053/j.gastro.2008.03.077.

https://doi.org/10.1017/S1751731119001794 Published online by Cambridge University Press