

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.

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

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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 mono-saccharides (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 homeostatic 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).

Table 1. Main simple carbohydrates receptors and transporters known to be involved in GIT sensing in humans and pigs¹

Nutrient	Gene	Receptor/transporter	Cell-type expression in gut tissues	GI peptides secreted	References ²
Gluc, Mal, Suc, Fru, sugar alcohols	<i>T1R2/T1R3</i>	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 <i>et al.</i> , 2002; Gerspach <i>et al.</i> , 2011; Moran <i>et al.</i> , 2010a
Gluc, Gal	<i>SGLT1/SGLT3</i>	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	Wright <i>et al.</i> , 2011; Röder <i>et al.</i> , 2014; Suga <i>et al.</i> , 2019; Moran <i>et al.</i> , 2010
Gluc, GalFru, Man, Glucos	<i>GLUT2</i>	Membrane transporter	Pancreatic β -cells, K-cells, L-cells, enterocytes	Glucagon, GLP-1, Insulin	Marty <i>et al.</i> , 2006; Zuo <i>et al.</i> , 2010; Mueckler and Thorens, 2013; Fournel <i>et al.</i> , 2016; Seino <i>et al.</i> , 2016
Gluc, Glucos	<i>GLUT4</i>	Membrane transporter	T1r3-positive taste cells	-	Yee <i>et al.</i> , 2011; Zhang <i>et al.</i> , 2016
Gluc, Fru, Gal	<i>GLUT5</i>	Membrane transporter	Apical membrane of enterocytes	-	Cottrell <i>et al.</i> , 2006; Douard and Ferraris, 2008
Gluc; Fru	<i>GLUT7</i>	Membrane transporter	Small intestine, colon	-	Cheeseman, 2008; Vigors <i>et al.</i> , 2016
Gluc, Fru	<i>GLUT9</i> ³	Urate, glucose sensor	Small intestine	-	Xuet <i>et al.</i> , 2016; Bu <i>et al.</i> , 2017
Gluc	<i>K_{ATP} channel</i>	Glucose sensor	Pancreatic β -cells, L-cells and K-cells	GIP, GLP-1, Insulin	Reimann and Gribble, 2002; McTaggart <i>et al.</i> , 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 heterotropic 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,

Table 2. Main AA receptors and transceptors known to be involved in GIT sensing in humans and pigs¹

AA and peptides	Gene	Receptor/transceptor	Cell-type expression in the GIT	GI peptides secreted	References ²
L-AA ³	<i>T1R1/T1R3</i>	Umami taste receptor	Taste buds, L and K-cells	CCK, Ghrelin	Stensels and Depoortere, 2018
Peptides, Lysophosphatidic acid	<i>GPR92 (GPR93/LPAR5)</i>	Peptone and LPA sensor	Gustatory sensory cells, G-cells, D-cells and GIT lymphocytes	CCK, Gastrin, Ghrelin	Haid <i>et al.</i> , 2012 and 2013; Kotarsky <i>et al.</i> , 2006
L-Phe and L-Trp, peptone	<i>CaSR</i>	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 <i>et al.</i> , 2015; Wang <i>et al.</i> , 2018; Zhao <i>et al.</i> , 2018; Modvig <i>et al.</i> , 2019
L- α -amino acids and divalent cations	<i>GPRC6A</i>	AA sensor	G-cells, D-cells, L-cells, pancreas, liver and gallbladder	GLP-1	Haid <i>et al.</i> , 2012; Oya <i>et al.</i> , 2013; Depoortere, 2014
L-Glutamic	<i>mGluR4, mGluR1</i>	L-glutamate receptor	Taste buds and enterocytes	-	Chaudhari <i>et al.</i> , 2000; Toyono <i>et al.</i> , 2003; Da Silva <i>et al.</i> , 2014
di-tripeptides	<i>PepT1, 2</i>	Peptide transport into cell	Apical microvilli enterocytes in small intestine	GLP-1	Vigors <i>et al.</i> , 2016; Modvig <i>et al.</i> , 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 transceptors 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 pTas1r1 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

Table 3. Main FFA receptors and transceptors known to be involved in GIT sensing in humans and pigs¹

Nutrient	Gene	Function	Cell-type expression in the GIT	GI peptides secreted	References ²
C1-C6	<i>FFAR2 (GPR43)</i>	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 <i>et al.</i> , 2011; Colombo <i>et al.</i> , 2012; Engelstof <i>et al.</i> , 2013; Brooks <i>et al.</i> , 2017
C1-C6	<i>FFAR3 (GPR41)</i>	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 <i>et al.</i> , 2009; Nøhret <i>et al.</i> , 2013; Li <i>et al.</i> , 2014; Chambers <i>et al.</i> , 2015
C4 C9-C14	<i>MCT1 (SLC16A1)</i> <i>GPR84</i>	Butyrate transporter Regulation of systemic energy metabolism, lipid sensor	Caco-2 cells colon Taste buds, oral granulocytes, G-cells (stomach), colon, liver	–	Haenen <i>et al.</i> , 2013; Stumpff, 2018 Da Silva <i>et al.</i> , 2014; Liu <i>et al.</i> , 2018; Widmayer <i>et al.</i> , 2017
C10-C22, saturated and unsaturated	<i>FFAR1 (GPR40)</i>	FFA taste receptor ³ and FFA sensing	Taste buds and L-cells, I-cells, pancreatic β -cells	CCK, insulin	Itoh <i>et al.</i> , 2003; Liou <i>et al.</i> , 2011b ; Da Silva <i>et al.</i> , 2014; Chen <i>et al.</i> , 2017
C12-C22, saturated and unsaturated	<i>FFAR4 (GPR120)</i>	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 <i>et al.</i> , 2012; Gonget <i>et al.</i> , 2013; Ichimura <i>et al.</i> , 2014; Iwasaki <i>et al.</i> , 2015
Long-chain FA	<i>FABP2</i>	FA transporter	Enterocytes K-cells	GIP	Besnard <i>et al.</i> , 2002; Vigors <i>et al.</i> , 2016
Long-chain FA	<i>FATP4</i>	FA transporter	Small intestine enterocytes,	CCK, secretin	Stahl <i>et al.</i> , 1999; Zong <i>et al.</i> , 2018
Long-chain FA	<i>CD36</i>	FA translocase, regulation of fat sensing	Apical side of lingual taste bud cells. Brush border membrane of enterocyte small intestine	GLP-2	Laugerette <i>et al.</i> , 2005; Yamamoto <i>et al.</i> , 2012; Vigors <i>et al.</i> , 2016
Propionate	<i>OLFR78⁴</i>	FA sensing	Colonic L-cells	PYY	Fleischer <i>et al.</i> , 2015
Butyrate	<i>OR51E1</i>	FA sensing	Stomach, pyloric, duodenal, jejunal, ileal, caecal, colonic and rectal mucosae L-cells	GLP-1, PYY	Priori <i>et al.</i> , 2015; Han <i>et al.</i> , 2018
2-monoglycerides	<i>GPR119⁴</i>	Enteroendocrine lipid sensor	L-cells, β -cells	GLP-1, PYY, insulin	Soga <i>et al.</i> , 2005; Overton <i>et al.</i> , 2006, Kogure <i>et al.</i> , 2011
Bile acids	<i>GPBAR1 (TGR5)</i>	Cell surface receptor for bile acids	Liver sinusoidal endothelial cells, gall bladder epithelial cells, kupffer cells, enteric neurons and cells	PYY, GLP-1	Poole <i>et al.</i> , 2010; Jain <i>et al.</i> , 2012; Dehmlow <i>et al.</i> , 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 known 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. oeloyethanolamide) 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 anorexigenic (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 MCFAs 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; Deloouse *et al.*, 2017a and

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 (Rozenfurt, 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.

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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