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Chemoreceptors in the Gut

S. Steensels and I. Depoortere

Translational Research Center for Gastrointestinal Disorders, KU Leuven, 3000 Leuven, Belgium; email: inge.depoortere@kuleuven.be

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Abstract

The gastrointestinal tract represents the largest interface between the human body and the external environment. It must continuously monitor and discriminate between nutrients that need to be assimilated and harmful substances that need to be expelled. The different cells of the gut epithelium are therefore equipped with a subtle chemosensory system that communicates the sensory information to several effector systems involved in the regulation of appetite, immune responses, and gastrointestinal motility. Disturbances or adaptations in the communication of this sensory information may contribute to the development or maintenance of disease. This is a new emerging research field in which perception of taste can be considered as a novel key player participating in the regulation of gut function. Specific diets or agonists that target these chemosensory signaling pathways may be considered as new therapeutic targets to tune adequate physiological processes in the gut in health and disease.

1. INTRODUCTION

Before ingestion, food is sensed by taste receptors on the tongue that transmit signals via sensory vagal afferents to inform the brain about the chemical composition of the meal (1). Sweet or umami tastants that help to identify energy-rich nutrients are sensed via heterodimers of subtypes of the taste 1 receptor family (TAS1R). Bitter, which signals the presence of potentially toxic compounds, is sensed by 25 subtypes of the taste 2 receptor family (TAS2R). The sour and salty tastes are sensed via ion channels and signal the presence of dietary acid present in spoiled foods or salts essential for maintaining the water balance of the body, respectively. It remains a matter of debate whether fatty acids elicit an independent taste perception.

Together with other sensory processes (e.g., oral texture, olfactory sensations, visual and cognitive effects), the brain will respond with learned anticipatory responses. These effects aid in the digestion, absorption, and metabolization of nutrients in a coordinated fashion, prior to nutrient absorption.

After ingestion of the meal, the gut, which forms the key interface between food and the human body, will also "taste" the macronutrient composition of the meal to elicit adequate motor and secretory responses to assimilate nutrients and eliminate waste products of the meal. Harmful contaminants in the food are also detected and elicit protective functions such as food aversion, vomiting, and inhibition of gastric emptying to avoid further food ingestion (2). The chemosensory systems involved are similar to those present in the lingual system and are present on several cell types in the gut epithelium, such as enterocytes, enteroendocrine cells (EECs), tuft cells, Paneth cells, goblet cells, microfold cells, and cup cells. The epithelium plays a prominent role in the communication between the lumen, subepithelium, afferent nerve fibers, and the brain to trigger adaptive responses that affect gastrointestinal function, food intake, glucose metabolism, and immune function.

This review summarizes our current knowledge on the interplay between chemosensors present in the gut epithelium and the activation of downstream effector pathways that regulate human health. Knowledge of the disturbances or adaptations that occur in chemosensing during disease may lead to the development of new gut-directed therapies.

2. EFFECTOR SYSTEMS THAT TRANSMIT SENSORY INFORMATION VIA CROSS TALK

2.1. Enterocytes

Enterocytes are absorptive cells and are the major cell type lining the gut. On their apical side, they contain microvilli to enlarge the luminal contact surface and express several transporters. The transporters involved in the sensing of nutrients and non-nutrients in enterocytes are depicted in **Figure 1*a***.

2.1.1. Sensing of nutrients. Enterocytes in the gut epithelium express several transporters that regulate the uptake of nutrient metabolites such as sugars, amino acids, and fatty acids.

2.1.1.1. Carbohydrates. Enterocytes predominantly transport carbohydrates out of the lumen of the small intestine as free glucose and fructose. Polysaccharides are first digested by α-amylases (in saliva and pancreatic fluids) to disaccharides, which are digested to monosaccharides by the brush border enzymes present in the enterocytes.

Glucose is transported across the apical membrane of the gut epithelium via active transport through the sodium-dependent glucose cotransporter 1 (SGLT1) and can be metabolized

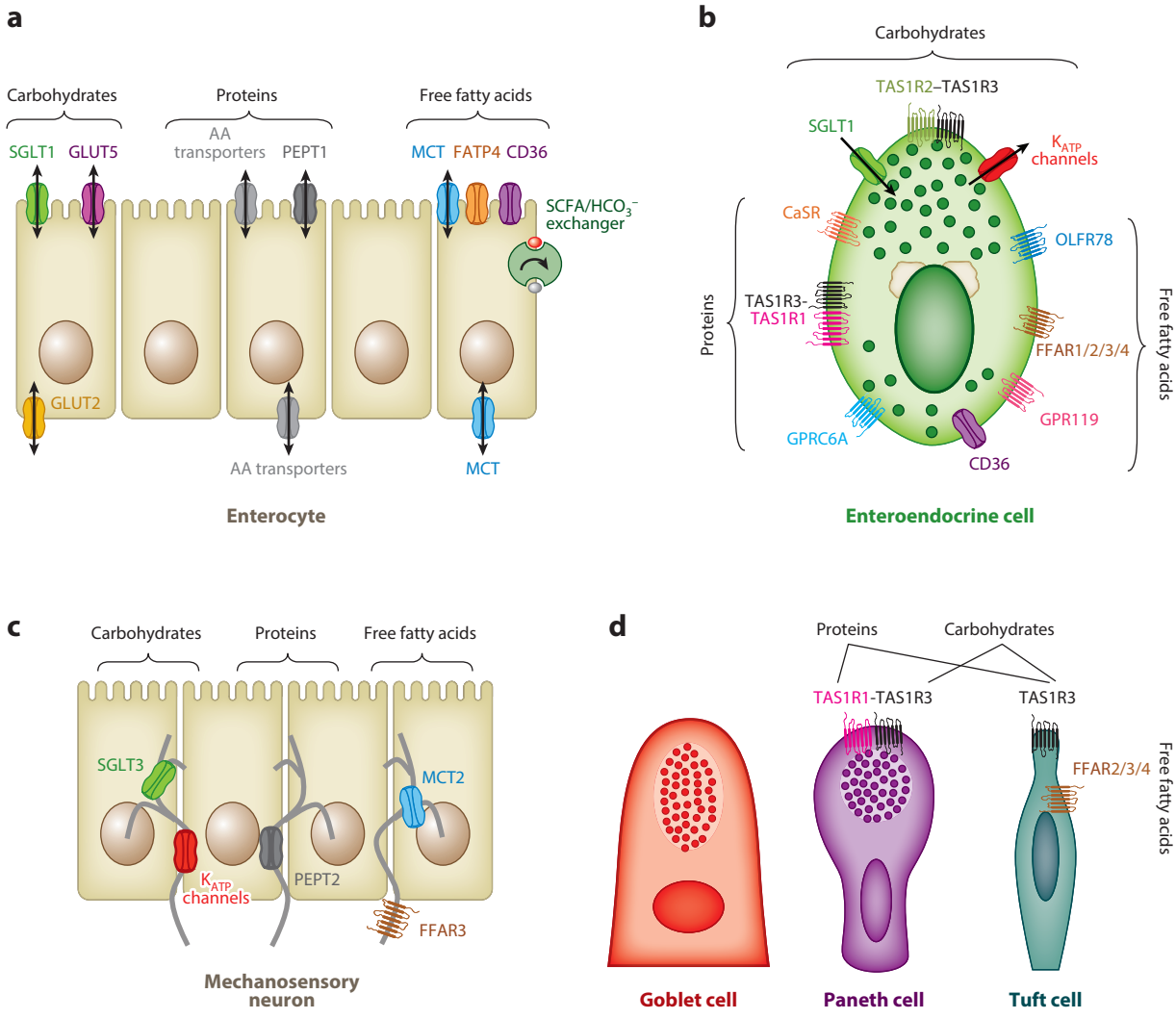

Figure 1

Schematic overview of the chemosensors in the different cell types of the gastrointestinal epithelium. Nutrients (carbohydrates, proteins, and fatty acids) are sensed by different receptors and/or transporters in (*a*) enterocytes, (*b*) enteroendocrine cells, (*c*) mechanosensory neurons, and (*d*) goblet cells, Paneth cells, and tuft cells. Abbreviations: AA, amino acid; CaSR, calcium-sensing receptor; CD36, cluster of differentiation 36; FATP4, fatty acid transport protein 4; FFAR1/2/3/4, free fatty acid receptor 1/2/3/4; GLUT2/5, glucose transporter 2/5; GPR119, G protein–coupled receptor 119; GPRC6A: G protein–coupled receptor family C group 6 member A; K_{ATP}, ATP-sensitive potassium; MCT, monocarboxylate transporter; OLFR78, olfactory receptor 78; PEPT1/2, peptide transporter 1/2; SCFA/HCO_3^-, short-chain fatty acid bicarbonate exchanger; SGLT1/3, sodium-dependent glucose cotransporter 1/3; TAS1R1/2/3, taste 1 receptor family member 1/2/3.

intracellularly. In a state of low luminal glucose concentrations, the passive glucose transporter 2 (GLUT2) transports glucose from the bloodstream into the enterocyte to ensure glucose metabolism. When in a state of high luminal glucose, GLUT2 will transport the excess glucose across the basolateral epithelial membrane (3). Strikingly, $GLUT2^{-/-}$ mice show only a modest reduction (4) or no reduction (5) in peripheral blood glucose levels after a high luminal

glucose bolus. These observations suggest the existence of an additional glucose transporter in the basolateral membrane.

GLUT2 can also translocate to the apical membrane during high luminal glucose concentrations that exceed the glucose absorption capacity of SGLT1 (6). The presence of apical GLUT2 was demonstrated in several in vitro and in vivo experiments in obese mice and human subjects, but these findings have been questioned by others (3). Indeed, studies in SGLT1$^{-/-}$ and GLUT2$^{-/-}$ mice point toward a predominant role for SGLT1 in apical glucose transport (4), and patients suffering from congenital GLUT2 deficiency (Fanconi-Bickel syndrome) do not display impaired luminal glucose absorption (7).

Fructose is transported across the apical membrane via the glucose transporter GLUT5 (8), but similar to glucose, it needs GLUT2 to be transported through the basolateral membrane into the bloodstream.

2.1.1.2. Proteins. Protein digestion and denaturation start in the acidic environment of the stomach, with pepsin as the primary proteolytic enzyme. Pancreatic proteases enhance protein degradation, and luminal peptides are further cleaved by peptidases at the brush border membrane of the enterocytes to generate free amino acids and di- and tripeptides. Whereas the amino acid transport is mediated by specific transporters, the uptake of di- and tripeptides is solely mediated by the high-capacity/low-affinity proton-dependent intestinal peptide transporter 1 (PEPT1) (3). Most peptides entering the cell will be hydrolyzed in the cytosol, followed by the export of free amino acids via different basolateral amino acid transporters.

2.1.1.3. Fatty acids. Free fatty acids (FFAs) are liberated from the lipid droplets in the small intestine by lipases and are incorporated into micelles that are transported to the surface of the enterocytes, which absorb FFAs via passive diffusion and protein-facilitated FFA transfer. Among the candidate FFA transporters in the intestine are cluster of differentiation 36 (CD36) and fatty acid transport protein 4 (FATP4), the latter of which has been identified as a major fatty acid transporter (9).

Although most free fatty acids are released during the digestion of dietary fat, short-chain fatty acids (SCFAs) (fatty acids with a carbon chain $\geq$6) are produced in the distal part of the intestine by colonic microbial fermentation of indigestible carbohydrates. The major SCFA products generated by the microbiome are acetate (C2), propionate (C3), and butyrate (C4). Most SCFAs are absorbed by the colonocytes via three different mechanisms: (*a*) passive diffusion of the protonated SCFA, (*b*) exchange with bicarbonate in a 1:1 ratio, or (*c*) active transport of the dissociated SCFAs via monocarboxylate transporters (MCTs). The electrogenic sodium-dependent monocarboxylate transporter 1 (SMCT1) and the MCTs (MCT1, MCT2, and MCT4) are found in the apical membrane of enterocytes and transport SCFAs (10). The absorbed SCFAs that are not completely metabolized by the colonocytes are transported across the basolateral membrane into the bloodstream via MCT4, MCT5, or the SCFA/HCO_3^- exchanger.

2.1.2. Sensing of non-nutrients. Enterocytes not only regulate nutrient uptake, but they can also mediate the uptake of several other compounds. For instance, they play an important role in the enterohepatic circulation of bile acids and have several efflux transporters in place to limit the absorption of toxic compounds.

2.1.2.1. Bile acids. Bile acids are amphipathic steroids synthesized from cholesterol in hepatocytes in the liver. Prior to secretion, bile acids are conjugated in the liver with glycine or taurine

to form primary bile acids. Bile is stored in the gallbladder and ultimately secreted into the intestine through the bile duct after an eating stimulus. In the colon, bile acids are modified by the commensal microbiota. First, bile acids are deconjugated, which renders the reabsorption of bile acids less efficient and thus promotes fecal bile acid excretion. Second, intestinal bacteria convert primary bile acids into secondary, more hydrophobic bile acids via 7 α-dehydroxylation. However, only a small amount of bile acids normally reaches the colon, as they are primarily reabsorbed by enterocytes in the small intestine and recycled back to the liver via the portal vein in a process called enterohepatic circulation. They can be absorbed through a combination of passive absorption in the proximal small intestine and active transport in the distal ileum. The apical sodium-dependent bile acid transporter plays a role in ileal bile acid transport (11). The bile acid–binding protein [I-BABP, also named fatty acid–binding protein 6 (FABP6)] facilitates ileal intracellular bile acid transport to the basolateral side of the enterocytes, where bile acids are secreted into the portal circulation via the organic solute transporter (OST)α/β heterodimer.

2.1.2.2. Bitter compounds. The efflux transporter, ATP-binding cassette B1 (ABCB1), is expressed on the apical membrane of intestinal epithelial cells to limit the absorption of toxic food substances, xenobiotics, and many chemotherapeutic agents that taste bitter (12). Bitter compounds may also limit their own absorption via paracrine signaling. For example, the bitter agonist phenylthiocarbamide (PTC) can induce cholecystokinin (CCK) release from EECs, which can upregulate the ABCB1 transporter on enterocytes, increasing its efflux activity and limiting PTC absorption (13).

2.2. Enteroendocrine Cells

EECs represent the largest endocrine organ in the body. They are scattered throughout the gastrointestinal (GI) tract but only comprise <1% of the gut epithelium. At least 12 subtypes of EECs secrete a wide range of peptides (>20) to affect a number of physiological processes involved in the regulation of food intake and gastrointestinal motility (14). Initially, these cells were classified based on the peptide they secrete, but recent evidence suggests that this dogma is no longer valid and that one cell type can secrete several hormones (15). Most EECs, with the exception of 5-HT, show a clear gradient in their distribution pattern. For instance, the stomach contains EECs that secrete ghrelin (P/D1-cells), somatostatin (D-cells), gastrin (G-cells), and histamine (ECL-cells), whereas CCK (I-cells), glucagon-like peptide-1 (GLP-1) (L-cells), peptide YY (PYY) (L-cells), and gastric inhibitory peptide (GIP) (K-cells), among others, are mainly produced in the small intestine and colon. EECs can be either the closed type that lack access to the gut lumen or the open type with microvilli on their apical membrane that extend to the lumen and come into direct contact with the macronutrients (16).

Hormones released by EECs can act locally on other cells (including immune cells) and on nerve endings in a paracrine fashion, or they can enter the circulation to act in an endocrine fashion at remote sites. Recent evidence suggests that nutrients can also directly interact with the nervous system via a neuroepithelial circuit. Indeed, three-dimensional reconstructions of L-cells and I-cells revealed that peptide-secreting vesicles in these EECs are contained within an axon-like basal process, called a neuropod, that appears to guide the secretion of hormones to neurons innervating the small intestine and colon (17).

2.2.1. Function of gut hormones. This review mainly focuses on the chemosensing mechanisms of the gut hormones ghrelin, GLP-1, PYY, and CCK, which play an important role in appetite regulation. Ghrelin acts as a hunger signal, whereas GLP-1, PYY, and CCK act as satiety signals.

2.2.1.1. Ghrelin. Ghrelin is mostly (80%) secreted by P/D1-cells (X/A-cells in rodents) from the stomach. Ghrelin is a 28-amino acid peptide with a unique posttranslational modification consisting of an octanoyl group at Ser3 that is necessary for the activation of its receptor (growth hormone secretagogue receptor) and thus for its biological activity. Ghrelin levels rise postprandially and decrease after the meal to dictate the timing of meals. Besides initiating food intake and influencing hunger on a short-term basis, ghrelin also promotes fat storage, resulting in increased body weight in the long term (18). Furthermore, ghrelin is an important gastroprokinetic agent.

2.2.1.2. GLP-1. The biologically active hormones GLP-$1_{7\text{-}37}$ and GLP-1_{7-36} amide are secreted from intestinal L-cells and are both equally potent at activating the GLP-1 receptor. These hormones are rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP4) to antagonists. GLP-1 levels increase after a meal to induce satiety, delay gastric emptying, and potentiate glucose-induced insulin secretion as an incretin hormone (19). These biological functions led to the development of GLP-1 mimetics for the treatment of type 2 diabetes.

2.2.1.3. PYY. PYY is a 36-amino acid peptide that is released from enteroendocrine L-cells in the distal gut. Full-length PYY acts on the Y-family receptors Y_1, Y_2, and Y_5, whereas degradation of PYY_{1-36} by DPP4 results in the generation of PYY_{3-36}, a selective agonist for the Y_2 receptor that inhibits food intake (20). In addition, PYY affects satiety by delaying gastric emptying and inducing the ileal brake to optimize nutrient digestion and absorption.

2.2.1.4. CCK. CCK is secreted from enteroendocrine I-cells in the small intestine. It circulates under several forms, each identified by the number of amino acids it contains (CCK58, CCK33, CCK22, and CCK8). CCK enhances meal digestion by triggering the release of digestive enzymes and bile from the pancreas and gallbladder, respectively (21). CCK decreases meal size and enhances satiety by delaying gastric emptying.

2.2.2. Sensing of nutrients. Chemosensors on EECs respond to meal-related stimuli to control the release of gut hormones that coordinate food intake, insulin release, and gut motility. The nutrient sensors present on EECs are summarized in **Table 1** and **Figure 1*b***.

2.2.2.1. Carbohydrates and sweeteners. Carbohydrate sensing mainly occurs on L-cells and K-cells that secrete the incretin hormones GLP-1 and GIP, respectively. The sweet taste receptor TAS1R2-TAS1R3, the glucose transporter SGLT1, and ATP-sensitive potassium (K_{ATP}) channels mediate glucose-induced GLP-1 secretion. Several lines of evidence support the role of a functional sweet taste receptor complex on L-cells. First, TAS1R2, TAS1R3, and α-gustducin, a gustatory G protein coupled to several taste receptors, are colocalized with L-cells in humans and rodents (22, 23). Second, the carbohydrates glucose and fructose and the artificial sweetener sucralose elicit GLP-1 secretion from mouse (GLUTag) and human (NCI-H716) EEC lines and mouse small intestinal explants (22, 24). Third, glucose-induced GLP-1 secretion is almost or completely impaired in knockout animals for α-gustducin or TAS1R3 or in the presence of a sweet taste receptor antagonist (22, 24). Finally, human studies using the sweet taste receptor antagonist lactisole showed the involvement of the sweet taste receptor in glucose-induced GLP-1 and PYY secretion but not in CCK release (23, 25). However, lactisole did not block the effect of a liquid meal consisting of proteins, fats, and other complex carbohydrates on GLP-1 and PYY release (25). Thus, although sweet taste receptors may play a role in the effect of glucose on GLP-1 and PYY release, their effect is likely overruled by other macronutrients in a meal.

Table 1 Overview of chemosensors on enteroendocrine cells along the gastrointestinal tract

	Enteroendocrine cells				
	X/A-cell	**G-cell**	**D-cell**	**I-cell**	**L-cell**
Gut hormone	Ghrelin	Gastrin	Somatostatin	CCK	GLP-1, PYY
Function	Food intake stimulation Adipogenesis Growth hormone release	Stimulation of acid secretion	Inhibition of gastrin release	Inhibition of food intake and gastric emptying Gallbladder contraction Stimulation of pancreatic enzyme secretion	Stimulation of insulin release (GLP-1) Inhibition of food intake and transit
Anatomic localization	Stomach	Stomach	Stomach, small intestine	Small intestine	Small intestine, colon
Nutrient sensors					
Carbohydrates and sweeteners	TAS1R3 SGLT1 K_{ATP} channels	NR	NR	NR	TAS1R2-TAS1R3 SGLT1 K_{ATP} channels
Proteins	CaSR GPRC6A TAS1R1-TAS1R3	CaSR GPRC6A LPA_5R	CaSR GPRC6A LPA_5R	CaSR TAS1R1-TAS1R3	GPRC6A TAS1R1-TAS1R3
Lipids	FFAR2 FFAR4	FFAR3	FFAR4	FFAR1 FFAR3 FFAR4 CD36	FFAR1 FFAR2 FFAR3 FFAR4 OLFR78 GPR119 FATP4
Non-nutrient sensors					
Bile acids	NR	NR	NR	NR	GBAR1 FXR
Bitter compounds	TAS2R	NR	NR	TAS2R	TAS2R
Phytochemicals	TRPA1	NR	NR	TRPA1	TRPA1 OR1G1
Microbial products	NR	NR	NR	TLRs	TLRs

Abbreviations: CaSR, calcium-sensing receptor; CCK, cholecystokinin; CD36, cluster of differentiation 36; FATP4, fatty acid transport protein 4; FFAR1/2/3/4, free fatty acid receptor 1/2/3/4; FXR, farnesoid-X-receptor; GBAR1, G protein–coupled bile acid receptor 1; GLP-1, glucagon-like peptide-1; GPR119, G protein–coupled receptor 119; GPRC6A, G protein–coupled receptor family C group 6 member A; K_{ATP}, ATP-sensitive potassium; LPA_5R, lysophosphatidic acid receptor 5; NR, not reported; OLFR78, olfactory receptor 78; OR1G1, olfactory receptor family 1 subfamily G member 1; PYY, peptide YY; SGLT1, sodium-dependent glucose cotransporter 1; TAS1R1/3, taste 1 receptor family member 1/3; TAS2R, taste 2 receptor family; TLR, Toll-like receptor; TRPA1, transient receptor potential cation channel subfamily A member 1.

Other evidence suggests that SGLT1 is colocalized with intestinal L-cells and acts as a transceptor (26). The role of this pathway has been confirmed in vitro using SGLT1 antagonists (27) and in vivo in SGLT1 knockout mice (28).

A third possible glucose sensor is the K_{ATP} channel. L-cells and K-cells express glucokinase and K_{ATP} channel subunits (29). This machinery couples glucose metabolism and subsequent ATP generation to the closure of K_{ATP} channel subunits and peptide release (30). A role for K_{ATP}

channels has been shown in vitro in L-cells using K_{ATP} channel blockers (26, 30), but this pathway was not confirmed in humans in vivo (31). Therefore, K_{ATP} channels may not be important for glucose-induced GLP-1 release. Studies in the ghrelinoma cell line and in ex vivo segments from α-gustducin knockout mice could not confirm a functional role for α-gustducin–mediated sweet taste receptor signaling in the effect of glucose and sweeteners on ghrelin release (32).

Although artificial sweeteners affect GLP-1 and ghrelin release in vitro (22, 32), no effects are observed in vivo in rodents and humans (33, 34). These results question the physiological relevance of the sweet taste receptor complex in gut hormone secretion.

It is important to note that not all sweet compounds bind to the same binding pocket of the sweet taste receptor heterodimer (35). Carbohydrates and artificial sweeteners are hence likely to activate a different signaling cascade, and although artificial sweeteners may not induce physiological effects, carbohydrates may still signal via the sweet taste receptor.

2.2.2.2. Proteins. Protein breakdown products such as di- and tripeptides are sensed via the lysophosphatidic acid receptor 5 (LPA_5R, also known as GPR92/93), whereas amino acids signal via several taste G protein–coupled receptors (GPCRs): the calcium-sensing receptor (CaSR), GPCR family C group 6 member A (GPRC6A), the heterodimer TAS1R1-TAS1R3, also known as the umami receptor or the metabotropic glutamate receptor, or a combination of these.

The CaSR mainly senses aromatic amino acids and Ca^{2+} and is expressed in X/A-, G-, I-, and D-cells (36, 37) (**Table 1**). The CaSR mediates the effect of L-phenylalanine (L-Phe) and L-alanine (L-Ala) on ghrelin release in a ghrelinoma cell line (38). In native I-cells and in secretin tumor cell line 1 (STC1) cells, CaSR coordinates the release of CCK in response to L-Phe and dietary peptides, respectively (39, 40).

GPRC6A, a receptor that predominantly senses basic amino acids and Ca^{2+}, acts in concert with the CaSR and is expressed in D-, G-, and L-cells (37, 41). L-ornithine stimulated GLP-1 secretion from GLUTag cells in a GPRC6A-mediated manner (41). However, in vivo studies using GPRC6A knockout mice could not confirm a role of GLP-1 in L-arginine– and L-ornithine–induced GLP-1 release (42).

TAS1R1-TAS1R3 is mainly activated by umami stimuli and glutamic and aspartic acids in humans, but in rodents, it broadly detects most of the 20 L-amino acids (43). Studies showed that TAS1R1-TAS1R3 plays a role in the secretion of CCK from STC1 cells and mouse proximal small intestinal tissue explants (44). Furthermore, the effect of monosodium glutamate and L-Ala on ghrelin release was mediated via TAS1R1-TAS1R3 in a ghrelinoma cell line (38).

Peptone, a protein hydrolysate, is likely sensed by LPA_5R and is expressed in G-cells and a subpopulation of D-cells (37). STC1 cells overexpressing LPA_5R amplified the effect of peptone on CCK transcription and release (45). In contrast, peptone-stimulated GLP-1 secretion was not impaired in colonic cultures from mice lacking LPA_5R (46) but was mediated via the CaSR and PEPT1 (46, 47). The latter does not seem to directly mediate peptone-induced CCK release in STC1 cells and in isolated CCK cells (48). Additionally, GPRC6A is involved in the effect of peptone on ghrelin release in a ghrelinoma cell line (38).

Collectively, these data suggest that sensing of amino acids and protein hydrolysates by EECs in the gut is finely tuned by different receptors and transporters that may play an important role in protein-induced satiety.

2.2.2.3. Lipids. Dietary triglycerides are digested by lipases to monoglycerides and FFAs that serve as an essential energy source but also function as signaling molecules that induce gut hormone release. FFAs are sensed by different free fatty acid receptors (FFARs), depending on their chain length.

Medium-chain (MCFA; 6–12C) and long-chain (LCFA; >12C) fatty acids are sensed via FFAR1 and FFAR4 on EECs but also by many other cell types, including immune cells, adipocytes, and pancreatic cells (49). FFAR1 knockout mice showed a reduced CCK, GLP-1, and GIP response after intragastric administration of LCFAs or after an acute oral fat diet (50, 51). FFAR4 is expressed in colonic L-cells and promotes GLP-1 secretion from STC1 cells in response to LCFAs (52). FFAR4, but not FFAR1, is present in gastric X/A-cells harvested from ghrelin–hrGFP (humanized *Renilla reniformis* green fluorescent protein) reporter mice, and FFAR4 activation decreased ghrelin release in vitro (36). Intragastric administration of an FFAR1 agonist did not affect ghrelin secretion, but the FFAR4 agonist unexpectedly increased ghrelin secretion (53). In vitro and in vivo studies in $CD36^{-/-}$ mice showed that CD36 also plays a role in FFA-mediated CCK and secretin removal (54).

Short-chain (<6C) fatty acids are sensed by FFAR2 and FFAR3. The SCFA receptors FFAR2 and FFAR3 are preferentially expressed in the distal intestine, where microbial fermentation continually produces SCFAs (10). Propionate and acetate trigger GLP-1 release from primary colonic cultures from wild-type (WT) mice, but this effect was markedly or slightly diminished in cultures from $FFAR2^{-/-}$ mice and $FFAR3^{-/-}$ mice, respectively (55). In contrast, an in vivo study showed that an acute dose of butyrate, but not of acetate or propionate, increased GLP-1 and PYY levels in WT mice, whereas no butyrate-induced gut hormone increase was observed in $FFAR3^{-/-}$ mice (56). The SCFAs can reach the ghrelin cells in the stomach via the bloodstream after luminal uptake. Acetate and propionate have been shown to inhibit ghrelin secretion through FFAR2 from primary gastric X/A-cells (36).

Olfactory receptor 78 (OLFR78) was also identified as a receptor for SCFAs and binds acetate and propionate, albeit with a lower affinity than FFAR2 and FFAR3 (57). OLFR78 is expressed in mouse colonic L-cells coexpressing GLP-1 and PYY (58).

Oleoylethanolamide (OEA), an endogenous fatty acid amide that acts as a peroxisome proliferator–activated receptor-alpha (PPAR-α) agonist, activates a variety of receptors, including GPR119 predominantly expressed on EECs and pancreatic cells (59). GPR119 full-body knockout and L-cell–specific GPR119 knockout showed dramatically decreased plasma GLP-1 levels after a lipid gavage (60, 61). Oleoylethanolamide and synthetic GPR119 ligands triggered GLP-1 secretion from primary colonic cultures but were less effective in the upper small intestine (61). The suppressive effect of oleoylethanolamide on food intake was not affected in GPR119 knockout mice, indicating that GPR119 does not mediate the hypophagic effect of oleoylethanolamide (60). In addition to GPR119, FATP4 also plays a role in the sensing of OEA. $FATP4^{-/-}$ mice showed a reduced GLP-1 response after ileal OEA administration (62). Finally, the fatty acid transporter CD36, which recognizes a wide variety of FFAs, and FATP4 also play a role in lipid-induced gut hormone secretion (54, 62).

Overall, FFA-induced signaling in the gut may contribute to the fat-induced effects on hunger by affecting the release of the orexigenic hormone ghrelin and contribute to satiety by releasing the anorexigenic hormones CCK and GLP-1. Furthermore, the relative distribution of lipid sensors might be linked to their biological role. Long- and medium-chain fatty acid sensors (FFAR1 and FFAR4) are present throughout the GI tract because these fatty acids have a dietary origin, and their uptake is less rapid compared to simple sugars, allowing them to also induce the release of satiating signals from more distal parts of the GI tract. In contrast, a major part of the intestinal SCFA content is produced by gut microbiota, explaining why SCFA sensors (FFAR2 and FFAR3) have a low expression in the proximal intestine and are predominantly found in the distal part of the intestine. OEA is not a dietary lipid, but it is produced in the small intestine following feeding by a biosynthesis process that is modulated by bile acids. The fact that OEA is introduced in a later stage in the gut could explain why the sensing of OEA is not present in the proximal small intestine.

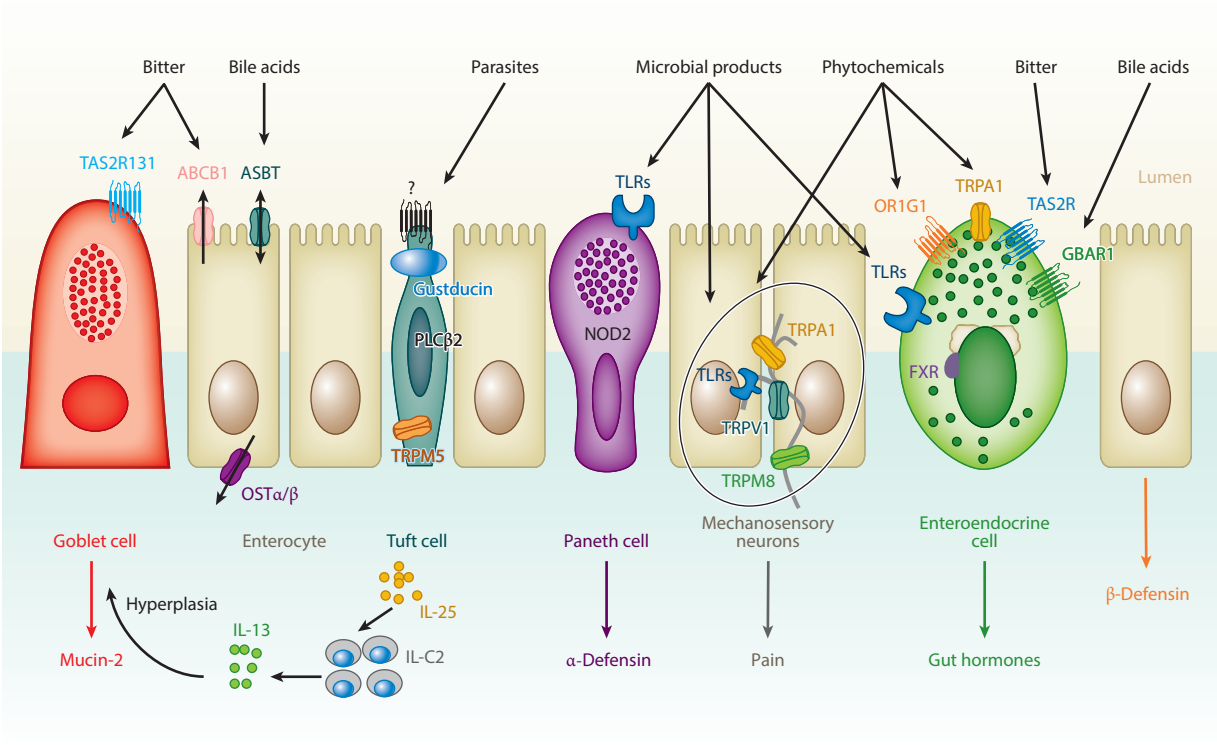

Figure 2

Schematic overview of chemosensors in the different cell types of the gastrointestinal epithelium. Non-nutrients (bitter compounds, bile acids, parasites, microbial products, and phytochemicals) are sensed by different receptors and/or transporters in several cell types of the epithelial lining to induce gut hormone release (enteroendocrine cells), immune responses (enterocytes, goblet cells, Paneth cells, and tuft cells), or pain sensation (mechanosensory neurons). Abbreviations: ABCB1, ATP-binding cassette B1; ASBT, apical sodium-dependent bile acid transporter; FXR, farnesoid X receptor; GBAR1, G protein–coupled bile acid receptor 1; IL, interleukin; NOD2, nucleotide-binding oligomerization domain–containing protein 2; OR1G1, olfactory receptor family 1 subfamily G member 1; OSTα/β, organic solute transporter α/β; PLCβ2, phospholipase C beta 2; TAS2R, taste 2 receptor family; TLR, Toll-like receptor; TRPA1, transient receptor potential cation channel subfamily A member 1; TRPM5/8, transient receptor potential cation channel subfamily M member 5/8; TRPV1, transient receptor potential cation channel subfamily V member 1.

2.2.3. Sensing of non-nutrients. Chemosensors on EECs will sense not only nutrients but also other compounds that could impact gut hormone release. For instance, EECs express receptors that allow bile acids to act in a hormone-like manner and contain bitter taste receptors that will detect and initiate the elimination of possible toxic compounds. The sensing mechanisms of non-nutrients by EECs are summarized in **Figure 2**.

2.2.3.1. Bile acids. In addition to their role in lipid absorption, bile acids also affect gut hormone release. They are the natural ligands for the G protein–coupled bile acid receptor 1 (GBAR1, also known as TGR5) and the nuclear farnesoid X receptor (FXR) through which bile acids play an important role in the regulation of energy and glucose homeostasis (63). Bile acids stimulate GLP-1 secretion through activation of GBAR1 on the basolateral membrane (64). In vitro and

in vivo studies with FXR agonists showed that FXR activation decreases proglucagon expression and GLP-1 secretion by inhibiting glycolysis (65).

2.2.3.2. Bitter compounds. Bitterness is sensed by the TAS2R family, which consists of approximately 30 members in vertebrates, ranging from only 3 receptors in chickens to ~50 in frogs (66). Humans have an intermediate repertoire of TAS2Rs, with 25 functional members. The members from the TAS2R family have a wide range of both activation threshold and tuning. For example, PTC only activates hTAS2R38, whereas diphenidol activates 15 different TAS2Rs.

The presence of TAS2R transcripts has been demonstrated in the gut mucosa of rodents and humans (67). TAS2R5 is colocalized with GLP-1–containing L-cells in the human small intestine (68). In the human colonic mucosa, TAS2R38 is colocalized with CCK-, PYY-, and GLP-1–containing EECs (69). The mouse (STC1) and human (NCI-H716) EEC lines express TAS2Rs and the full canonical taste signaling pathway, and several bitter agonists induce Ca^{2+} responses and affect gut peptide (CCK, GLP-1) release in these cells (66, 67). Gavage of denatonium benzoate increased glucose-induced GLP-1 secretion in *db/db* mice and lowered glucose levels (70).

Some bitter-tasting herbal medicines (e.g., berberine, *Hoodia gordonii*, *Gentiana scabra* root) have been shown to affect the release of anorexigenic gut peptides (GLP-1, CCK) in EEC lines and to possess antidiabetic activity in animal models of diabetes, but the exact nature of the bitter compounds involved needs to be determined (66).

Intragastric administration of bitter agonists in mice resulted in a short-term increase in plasma ghrelin levels and food intake (71). Bitter-sensing flavanols induce a short-term stimulation of ghrelin in rats, whereas subchronic treatment inhibited ghrelin release (72). The grape-seed phenolic extracts are composed of several molecules with different bioavailability and opposite effects. In vitro studies with the main molecules of the extract confirmed that monomeric flavanols stimulate ghrelin secretion, whereas oligomeric flavanols and gallic acid inhibit ghrelin secretion (72).

Together, these results indicate that the EECs are able to sense bitter tastants. The release of anorexigenic gut peptides in response to bitterness can be considered as an additional defense mechanism to limit further ingestion of toxic compounds if bitter sensing on the tongue fails as a first barrier.

2.2.3.3. Phytochemicals. EECs also sense phytochemicals derived from herbs and spices that are commonly included in our foods. An important family of phytochemical receptors comprises the transient receptor potassium (TRP) channel receptors consisting of 28 members in mammals (73).

Transient receptor potential cation channel subfamily A member 1 (TRPA1) is colocalized with 5-HT and ghrelin (74, 75) and enriched in L-cells of the murine small intestine (76). Phytochemicals that activate this receptor include allyl isothiocyanate (AITC, responsible for the pungent taste of wasabi and mustard), cinnamaldehyde (cinnamon), and capsaicin (73). AITC induced CCK and 5-HT release from STC1 and RIN14B cells, respectively (74, 77). Furthermore, TRPA1 activation increased GLP-1 secretion from primary murine intestinal cultures and GLUTag cells, an effect that was abolished in cultures from $TRPA1^{-/-}$ mice or by pharmacological TRPA1 inhibition (76). However, in vivo, the TRPA1 agonists methyl syringate and cinnamaldehyde did not alter GLP-1 but increased PYY levels after an oral administration, which was abolished after pharmacological TRPA1 inhibition (78). In the ghrelinoma cell line MGN3-1, cinnamaldehyde inhibited ghrelin release in a TRPA1-dependent manner (75).

In humans, an intraduodenal infusion of the TRPV1 agonist capsaicin significantly increased satiety but did not affect plasma GLP-1 and PYY concentrations in healthy volunteers (79). In contrast, a lunch containing capsaicin did increase GLP-1 and tended to decrease ghrelin levels but did not affect plasma PYY levels compared to a control lunch (80).

Phytochemicals can also activate odorant receptors on EECs. One such receptor is olfactory receptor 1G1, which is sensitive to thymol, the major compound present in thyme; it also increases serotonin release (81).

Phytochemicals should not be overlooked when addressing chemosensing in the gut because they are commonly included in food spices and herbs and affect gut hormone release. However, the enormous choice of receptors that can potentially play a role may limit specificity.

2.2.3.4. Microbial products. Several studies in germ-free mice have shown an active role for the gut microbiota in regulating energy homeostasis of the host (82). In addition to influencing the host metabolism directly (decreasing de novo hepatic lipogenesis and increasing systemic lipolysis), the conversion of dietary components by intestinal bacteria leads to the formation of a large variety of metabolites that affect gut hormone levels by altering nutrient sensor expression on EECs.

Indeed, germ-free mice showed reduced expression of CCK, GLP-1, and PYY accompanied by a decreased intestinal expression of the fatty acid sensors FFAR1, FFAR4, and CD36 and an upregulation of the glucose/umami sensors TAS1R3 and SGLT1 (83, 84). Thus, SCFAs produced by the microbiota and other small bioactive compounds are important key metabolites in transducing metabolic effects.

The gut microbiota also plays a role in the formation of secondary bile acids that activate bile acid receptors (GBAR1 and FXR) on EECs and produce bacterial endotoxins, which are best characterized for their inflammatory function, mediated through the activation of Toll-like receptors (TLRs). These TLRs are colocalized with serotonin in the human colon (85). In STC1 cells, lipopolysaccharide (LPS), a main constituent of the membrane of gram-negative bacteria, activated downstream mediators of TLR signaling and increased CCK secretion (85). Moreover, TLR agonists increased the expression of PYY but not of proglucagon in NCI-H716 cells in a nuclear factor-kappa B (NF-κB)–dependent manner (86).

Microbial metabolization also results in the production of other metabolites: (*a*) trimethylamine, which is metabolized from carnitine and choline in red meat and promotes cardiovascular disease; (*b*) ethylphenyl sulfate, which exacerbates autistic behavior in a mouse model; (*c*) indole propionic acid, which improves the gut epithelial barrier; and (*d*) indoxyl sulfate and *p*-cresyl sulfate, both of which are associated with poor cardiovascular outcome (87).

2.3. Mechanosensory Neurons

Gut sensations start with visceral sensory neurons. Extrinsic sensory pathways (vagal, thoracolumbar, lumbosacral, and viscerofugal) terminate in the gut and convey mechano- and chemosensory signals to target tissues within and outside the intestine to impact physiology and behavior (88). Extrinsic sensory neurons can be classified by the arrangement and morphology of their nerve endings into five subgroups: neurons with intraganglionic laminar endings, mucosal afferents, muscular-mucosal afferents, intramuscular arrays, and vascular afferents (88). In addition, the gut is the only organ that contains its own intrinsic nervous system, the enteric nervous system (ENS). The ENS is often referred to as the second brain because it continues to function even when the primary neural connection with the vagus nerve is severed. The ENS also contains sensory neurons, which are intrinsic primary afferent neurons that respond to mechanical and chemical stimuli and regulate the appropriate output to muscle and secretory motor neurons. According to their electrophysiological properties, enteric sensory neurons are classified as AH neurons, whereas S neurons function as moto- and interneurons.

2.3.1. Sensing of nutrients. Sensory nerve terminals of extrinsic and intrinsic origin do not penetrate the epithelium and therefore mainly sense nutrients via the release of gut hormones

that monitor the luminal content through nutrient sensors. For instance, nutrient-induced 5-HT release activates intrinsic AH neurons with terminals in the submucosal layer (89).

K_{ATP} channels and SGLT3 may function as glucose sensors in enteric neurons (90, 91), whereas the peptide transporter PEPT2 mediates uptake of dipeptides in mouse enteric glial cells and in intrinsic primary afferent neurons of the guinea pig ileum and colon (**Figure 1*c***) (92). It should be noted that amino acids such as cysteine and arginine are substrates for enzymes involved in the synthesis of the enteric neurotransmitters nitric oxide and hydrogen sulfide and may influence ENS activity indirectly. In addition, FFAR3 receptors are expressed in enteric neurons (93). In vitro studies in primary cultures of enteric neurons and in vivo studies with intrathecal perfusion showed that butyrate increased the proportion of cholinergic neurons in rats via an MCT2 transporter on enteric neurons to enhance colonic transit (94).

Whereas nutrient sensing by the ENS mainly serves to control motility, secretion, and blood flow in response to the presence of food in the lumen, nutrient sensing by extrinsic sensory nerves mainly serves to monitor the metabolic state and to relay hunger and satiety signals (95). Using more advanced technologies, a recent study determined how extrinsic sensory neurons detect stretch and nutrients in the gut and signal to the brain (96). It was shown that vagal GLP-1 receptor (GLP1R) neurons projected to intraganglionic laminar endings in stomach muscle and functioned as gastric mechanoreceptors. A second cohort of vagal GLP1R neurons responded to intestinal distension. In contrast, most of the sensory neurons that innervate the duodenal villi, adjacent to the pyloric sphincter, encoded the orphan receptor GPR65 but not GLP1R and responded to intestinal nutrients (glucose, glutamate, fatty acids, salt, and low pH but not to the artificial sweetener saccharin) (96). GPR65 neurons responded to serotonin but not to GLP-1 and CCK, which activated vagal GLP1R neurons. Optogenetic stimulation of GPR65 neurons inhibited gastric contractions, whereas activation of vagal GLP1R neurons increased gastric pressure. Thus serotonin-responsive vagal GPR65 neurons initiate an intestine–brain–stomach circuit that induces a feedback blockade of gastric motility to regulate the pulsatile rhythm of food entry into the intestine (96).

Furthermore, vagal GLP1R and GPR65 neurons target adjacent but distinct subregions of the nucleus tractus solitarius (NTS) in the brainstem providing evidence for a topographical NTS map linked to physiological input (96). These findings suggest that the vagus nerve shows many similarities with gustatory nerves to encode peripheral information. Indeed, also in taste buds, each taste receptor cell is specifically tuned to detect one taste quality and in turn will transmit its information to a designated ascending gustatory nerve fiber (97).

2.3.2. Sensing of non-nutrients. Mechanosensory nerve terminals also detect noxious irritants that will result in a painful sensation. The non-nutrient sensors of mechanosensory neurons are depicted in **Figure 2**.

2.3.2.1. Phytochemicals. Whereas vagal afferents mainly convey physiological information, spinal afferents respond beyond the physiological range and signal potential tissue damage induced by inflammation, injury, or ischemia by responding to noxious irritants released from different cell types. These chemicals activate specific ion channels and receptors called spinal nociceptors and increase sensitization and nociceptive activity. For instance, the transient receptor potential cation channel subfamily V member 1 (TRPV1) (heat, chili pepper, acid), TRPA1 (mustard oil, cinnamon), and TRPM8 (cold, menthol) channels are expressed in primary sensory neurons and afferent nerve endings in the GI tract (98). In contrast to its widely known expression in the afferent nerve fibers, the expression of TRPV1 in the ENS remains a matter of debate (99).

2.3.2.2. Microbial products. TLRs are expressed in dorsal root ganglia and regulate pain (100). MyD88, which mediates TLR signaling, is expressed by $Na_v1.8^+$ primary sensory neurons and plays an important role in interleukin (IL) 1-beta signaling. This contributes to persistent inflammatory pain and neuropathic pain in the maintenance phase. TLRs are also expressed in the ENS and integrate various microbial signals into a tailored response depending on the stimulated TLR (101).

2.4. Tuft Cells

Höfer et al. (102) provided the first evidence for the presence of the gustatory G protein α-gustducin in tuft cells, which are also known as brush cells or caveolated cells of the gut epithelium. With this finding, the concept that chemosensing is important for the coordination of gastrointestinal functions after food intake was born. Similar to the taste receptor cells, tuft cells are pear shaped with a tuft of microvilli at their apical side, which allows them to sense the luminal content. In contrast to taste receptor cells, which are clustered in taste buds on the tongue, tuft cells in the epithelial layer of the gut are solitary chemosensory cells. Tuft cells represent approximately 0.4% of the epithelial cells, but despite their chemosensory function, this cell type remained an enigmatic cell type until recently. The sensors of nutrients and non-nutrients on tuft cells are depicted in **Figures 1*d*** and **2**.

2.4.1. Sensing of nutrients. In the mouse stomach, α-gustducin–positive tuft cells are highly expressed at the limiting ridge, the boundary between the fundus and the corpus (103). Because rodents do not vomit, chemosensing in this region might be of utmost importance to prevent the ingestion of toxic compounds. These tuft cells also express phosphoinositide-specific phospholipase C beta 2 (PLCβ2), TRPM5, TAS1R3, and the lipid sensors FFAR2–FFAR4 (53, 104–106). Tuft cells have been found in close proximity to ghrelin- and serotonin-containing EECs, which are of the closed type and lack contact with the stomach lumen. Tuft cells have the capacity to generate two types of signaling molecules, acetylcholine and nitric oxide, which may propagate detected taste signals to closed EECs to adapt hormone secretion (105).

In the duodenal villi, tuft cells coexpress TAS1R1, TAS1R3, α-gustducin, and TRPM5, suggesting that they are involved in L-amino acid detection (107). In the colon, only the expression of gustducin and TRPM5 has been demonstrated.

2.4.2. Sensing of non-nutrients. Although the exact physiological role of tuft cells remained enigmatic for several years, three recent independent studies suggest that they play an important role in the induction of type 2 immunity to parasites.

2.4.2.1. Bitter compounds. Schütz et al. (108) showed that tuft cells in the colon responded with a rise in intracellular Ca^{2+} to stimulation with the bitter agonist denatonium benzoate. The signal was communicated to adjacent epithelial cells that responded with a delayed Ca^{2+} response, probably via the release of acetylcholine by the cholinergic tuft cells. Similar responses to bitterness have been reported in tuft cells of the trachea, urethra, and nasal epithelium (66). Nevertheless, TAS2Rs have not yet been demonstrated on tuft cells in the gut.

2.4.2.2. Parasites. Three recent publications show that molecules secreted during infection with parasitic worms such as helminths or protozoa are sensed via tuft cells expressing TRPM5 and α-gustducin and orchestrate type 2 cell–mediated immunity (109–111). Using a variety of transgenic mice, these authors show that tuft cells release IL-25, which further activates type 2 innate

lymphoid cells to secrete IL-13. This cytokine acts on epithelial crypt progenitors to promote differentiation of tuft cells and goblet cells, which is made possible by altering Notch signaling. The resulting tuft cell hyperplasia and concurrent goblet cell hyperplasia promote worm expulsion. In addition, IL-13 is known to induce STAT6-dependent changes in smooth muscle contractility that further promotes worm clearance (112). It is still unclear which infection-induced molecules are sensed by the taste receptors on tuft cells (sweet, bitter, or umami) to initiate this signaling cascade.

2.5. Goblet Cells and Paneth Cells

The colon is protected against the enormous bacterial load by a protective inner-attached sterile mucus layer that keeps the bacteria at a distance from the epithelial cells. Disturbance of the equilibrium may lead to inflammatory responses against the commensal bacteria, such as in ulcerative colitis (113). Goblet cells are scattered throughout the epithelium and produce the gel-forming glycosylated mucin-2 to form the protective mucus layer (114). Embedded in this mucin layer are cationic α- and β-defensin peptides, which are effective in killing a broad range of bacteria and have immune modulatory functions. In the small intestine, Paneth cells secrete α-defensins (HD5 and HD6), whereas β-defensins (hBD1, hBD2) are present in a variety of epithelial cells, including enterocytes (115). Paneth cells are thus specialized innate defense cells of the small intestine that regulate microbial density and protect nearby stem cells. The nutrient and non-nutrient sensors present on goblet and Paneth cells are depicted in **Figures 1*d*** and **2**.

2.5.1. Sensing of nutrients. TAS1R1 and TAS1R3 were demonstrated in the secretory granules of the Paneth cells at the bottom of the crypts and were colocalized with α-transducin but less frequently with α-gustducin, implying that α-transducin might play an important role as a taste G protein in these cells (116). PLCβ2 was not observed in secretory granules but in the cytoplasm of the Paneth cells. Expression of TAS1Rs on goblet cells has not been demonstrated.

2.5.2. Sensing of non-nutrients. Few studies have investigated the expression and role of chemosensors for non-nutrients in secretory cells, but evidence suggests that the sensing of bacterial products is of importance for the secretion of antimicrobial peptides from Paneth cells.

2.5.2.1. Bitter compounds. Using a TAS2R131 knockin mouse strain (Tas2r131$^{F/MBLF/M\text{-}IRES\text{-}Cre}$ mice), Prandi et al. (117) showed the presence of TAS2R131 on goblet cells in the colon, where they may play a role in the protection against harmful xenobiotics by stimulating the production of mucin.

Activation of TAS2Rs by bitter compounds has been linked to the secretion of antimicrobial peptides (β-defensins) in human primary sinonasal cultures that were capable of killing a variety of respiratory pathogens (118).

2.5.2.2. Microbial products. Bacterial products are detected by TLRs and nucleotide-binding oligomerization domain–containing proteins (NODs) to activate local defense mechanisms. TLRs and NOD2 are present on Paneth cells that secrete antimicrobial peptides after exposure to bacteria or bacterial antigens (119, 120). Expression of enteric α-defensin mRNA is reduced in terminal ileal biopsies from patients with Crohn's disease, with reduced expression being more pronounced in the presence of NOD2 mutations. This indicates a possible link between defective NOD2 protein in Paneth cells and the development of small bowel Crohn's disease (121).

3. CHEMOSENSORY SIGNALING AND DISEASE

3.1. Chemosensors and Metabolic Disorders

When the chemosensory information becomes disturbed, the gut may become maladapted to external cues, thus leading to the development or maintenance of diseases. Disturbances in gut chemosensory function have been implicated in the setting of obesity, diabetes, and immune-related diseases.

3.1.1. Can chemosensing reset obesity? The easy access to tasty, energy-dense foods contributes to the rise in obesity prevalence. This is reinforced by the enhanced sensory appeal for highly palatable foods rich in sugars/fats in obese patients. Oral detection of dietary lipids and sweet tastants is compromised by obesity in rodents (122, 123). In humans, the relation between body mass index and oral lipid sensitivity remains a matter of debate, but it is tempting to speculate that an inverse association might lead to an overconsumption of fatty foods because low-fat tasters consume more lipids than high-fat tasters (124). Evidence also indicates a heightened preference for sweet substances in obese individuals, which may drive the consumption of excess calories from carbohydrates (125). In contrast, obese patients that have undergone Roux-en-Y gastric bypass surgery have a reduced desire to consume high-fat and sweet foods (126).

Changes in the expression of chemosensory receptors both on the taste buds and along the GI tract could be part of an adaptive response mechanism adjusting the body to a sustained positive energy balance. Indeed, Stewart et al. (124) reported that the ability to sense oleic acid was compromised not only in the oral cavity of obese subjects but also in their GI tract. This resulted in a reduced motor response to oleic acid and a tendency for a delay in CCK release. In fact, Little et al. (127) showed altered expression of FFAR transcripts (CD36, FFAR4, GPR119) in the duodenum and a reduced number of I- and L-cells in obese patients. It was suggested that this may underlie the decreased GI hormone responses to fat and the disturbed regulation of energy intake in obese patients. In addition, genetic variations within the *CD36* gene locus have been associated with measures of whole-body adiposity but not with insulin sensitivity (128).

The SCFA receptors FFAR2 and FFAR3 may also pose a new therapeutic strategy for the treatment of obesity. Daily intragastric administration of the prebiotic fiber oligofructose for two months in mice on a high-fat diet decreased body weight gain but did not improve glucose intolerance (33). Supplementation of an inulin-propionate ester (which was used as a site-specific delivery vehicle for colonic propionate) to overweight subjects during 24 weeks reduced weight gain and prevented the deterioration in insulin sensitivity compared to the inulin-control group (129). Furthermore, the delivery site of the SCFAs was shown to be important because targeted distal, but not proximal, colonic infusions of acetate increased fasting fat oxidation, PYY levels, and concentrations of postprandial glucose and insulin (130). These results suggest that targeted colonic delivery of acetate/propionate or selective FFAR2 and FFAR3 agonists might be useful to treat obesity.

Variation in bitter taste receptor genes is also linked to differences in taste perception and might thus be a determinant in food preference. The best-characterized example is the PAV/AVI polymorphism in the *TAS2R38* gene, which determines whether a person will perceive the bitter taste of PTC and propylthiouracil. This polymorphism has been shown to be associated with eating behavior in a cohort of Amish women (131). *TAS2R38* is also upregulated on CCK-, GLP-1-, and PYY-containing EECs in diet-induced obese mice and in colonic biopsies from overweight/obese patients (69, 132). The altered *TAS2R38* expression might represent an adaptation of the GI mucosa to intraluminal changes induced by nutrient excess to regulate gut hormone release and body weight. Avau et al. (133) showed that intragastric treatment with quinine or denatonium

benzoate during one month decreased body weight gain in high-fat diet–induced obese mice in an α-gustducin–dependent manner. Nevertheless, the effect was not due to changes in gut peptide release, but a possible effect on adipocyte metabolism was suggested because TAS2Rs are expressed in adipose tissue and inhibited the differentiation of 3T3-F442A preadipocytes.

TAS2Rs are present not only on EECs but also in smooth muscle cells of the human and mouse gut; together, they regulate gastrointestinal motility and appetite (134). Indeed, intragastric administration of denatonium benzoate inhibited gastric emptying in mice, which was correlated with a decrease in food intake (71). In humans, bitter administration also impaired fundic relaxation after a liquid meal and was associated with increased satiation during an oral nutrient challenge (134). In the fasting state, intragastric administration of bitter compounds in healthy volunteers decreased antral motility and hunger ratings, possibly by decreasing motilin release (135). In general, targeting extraoral chemosensors might be an interesting therapeutic strategy to combat obesity.

3.1.2. Can we target chemosensors to resolve diabetes? The potential ramifications of faulty taste receptors are not limited to obesity. Polymorphisms upstream of the promotor region of the sweet taste receptor subunit TAS1R3 and in the α-subunit of the gustatory G protein gustducin have been associated with the variation in human sucrose sensitivity (136, 137). The expression of the intestinal sweet taste receptor subunit TAS1R2 was downregulated in response to intraduodenal glucose infusion during hyperglycemia in healthy volunteers but upregulated in nonobese patients with type 2 diabetes (138). This defect enhanced glucose absorption in patients with type 2 diabetes and may exacerbate postprandial hyperglycemia. In contrast, the increased glucose absorption in the proximal intestine of nondiabetic morbidly obese subjects was not related to changes in TAS1R2 expression but was related to increased SGLT1 expression (139). Intraduodenal glucose increased GIP and glucagon levels but not GLP-1 levels. This incretin profile promoted hyperglycemia and hyperinsulinemia. Thus, taste receptors as well as the modulation of glucose transporters should be considered as important therapeutic targets. Despite several efforts, only a few dual SGLT1/2 or selective SGLT1 compounds have advanced to clinical trials. The dual SGLT1/SGLT2 inhibitor LX4211 improved glycemic control in patients with type 2 diabetes on metformin monotherapy and decreased body weight and systolic blood pressure (140).

Previous studies in TAS1R3$^{-/-}$ and α-gustducin$^{-/-}$ mice suggest a relationship between the activation of TAS1R2-TAS1R3 in the L-cells, increased expression of glucose transporters, and consequently, increased glucose transport in enterocytes (24). These results caution against the use of artificial sweeteners in weight loss strategies. In fact, artificial sweeteners were recently shown to induce glucose intolerance in healthy subjects by inducing dysbiosis of the gut microbiota (141). In contrast, two recent randomized controlled trials showed that replacing sugar-sweetened beverages with noncaloric beverages might be a useful strategy in the battle against obesity (142, 143).

Targeting of FFARs in the gut has been proposed as a potential strategy for pharmacotherapy of type 2 diabetes. FFAR1 agonists have direct effects on β-cells and also enhance insulin secretion indirectly by affecting the release of incretins from EECs (144). However, there is also evidence that antagonists should be used instead of agonists because FFAR1 also seems to play a role in the deleterious effects of FFAs on β-cells (145). Despite promising results with the FFAR1 agonist TAK-875 in phase II trials on glycemia in diabetics, the phase III trials were discontinued due to hepatotoxic effects (146).

FFAR4 exon sequencing in obese individuals revealed a loss of function mutation in FFAR4 (p.R270H) that increased the risk of obesity, increased blood glucose levels, and diabetes (147, 148). FFAR4 not only affects incretin release in the gut but alleviates chronic inflammation associated with diabetes due to its effect on macrophages (146). Several FFAR4 agonists are being developed

to modulate metabolic homeostasis, but no agonists are currently being tested in clinical trials (146). Many pharmaceutical companies have been active in the search for GPR119 agonists; however, none has progressed beyond phase II studies (149).

3.2. Chemosensors and Immune Responses

Defects in innate immune responses, together with genetic predisposition, environmental risk factors, and gut microbiota, play an important role in the development of inflammatory bowel disease (IBD), such as Crohn's disease and ulcerative colitis. The production of α-defensins by Paneth cells is reduced in ileal Crohn's disease, and the mucus layer is deficient in ulcerative colitis due to goblet cell depletion (113). Because tuft cells mediate goblet cell hyperplasia through the production of IL-13, it cannot be excluded that defects in tuft cells may underlie goblet cell depletion in patients with ulcerative colitis (109–111). In fact, mice that are specifically deficient in intestinal epithelial Dclk1, a marker for tuft cells, show exacerbated injury to dextran sulfate sodium–induced colitis (150). As outlined previously, Paneth, goblet, and tuft cells all contain elements of the taste chemosensory signaling pathways. It is therefore tempting to speculate that targeting this signaling cascade might be useful to improve innate immunity in patients with IBD. Furthermore, microbial by-products such as SCFAs have been shown to exert anti-inflammatory effects. FFAR2 is highly expressed on leukocytes, and SCFAs protect against colitis in an FFAR2-dependent manner in mice (93, 151). Additionally, the SCFAs can directly promote peripheral regulatory T-cell generation independent of GPCR activation (152).

The MCFA receptor GPR84 is also highly expressed on macrophages and neutrophils. In contrast to SCFAs, MCFAs seem to have proinflammatory effects, as they enhance LPS-induced IL-12 and tumor necrosis factor alpha expression in macrophages (153).

Mice lacking the bile acid receptor GBAR1 were more susceptible to LPS-induced acute gastric inflammation compared to WT mice. GBAR1 activation inhibits gastric inflammation through antagonizing the NF-κB signaling pathway (154).

4. FUTURE PERSPECTIVES

The aforementioned findings support the existence of a functional continuum along the orointestinal tract that permanently senses ingested nutrients and non-nutrients to control ingestion, digestion, absorption, and the metabolic fate of energy nutrients. Taste buds and cells in the gut epithelium share common sensors, express similar hormones and receptors, and are connected to gustatory and vagal afferent nerve fibers involved in feeding behavior.

The discovery of new therapeutic targets may benefit from progress made on chemosensing in both the lingual and gastrointestinal systems. In view of the multitude of chemoreceptors and the region in the continuum that can be affected by disease, tailoring of treatment may be warranted.

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LITERATURE CITED

1. Chaudhari N, Roper SD. 2010. The cell biology of taste. *J. Cell Biol.* 190:285–96
2. Depoortere I. 2014. Taste receptors of the gut: emerging roles in health and disease. *Gut* 63:179–90
3. Daniel H, Zietek T. 2015. Taste and move: glucose and peptide transporters in the gastrointestinal tract. *Exp. Physiol.* 100:1441–50
4. Röder PV, Geillinger KE, Zietek TS, Thorens B, Koepsell H, Daniel H. 2014. The role of SGLT1 and GLUT2 in intestinal glucose transport and sensing. *PLOS ONE* 9:e89977
5. Stümpel F, Burcelin R, Jungermann K, Thorens B. 2001. Normal kinetics of intestinal glucose absorption in the absence of GLUT2: evidence for a transport pathway requiring glucose phosphorylation and transfer into the endoplasmic reticulum. *PNAS* 98:11330–35
6. Kellett GL, Helliwell PA. 2000. The diffusive component of intestinal glucose absorption is mediated by the glucose-induced recruitment of GLUT2 to the brush-border membrane. *Biochem. J.* 350(Pt. 1):155–62
7. Santer R, Hillebrand G, Steinmann B, Schaub J. 2003. Intestinal glucose transport: evidence for a membrane traffic-based pathway in humans. *Gastroenterology* 124:34–39
8. Burant CF, Takeda J, Brot-Laroche E, Bell GI, Davidson NO. 1992. Fructose transporter in human spermatozoa and small intestine is GLUT5. *J. Biol. Chem.* 267:14523–26
9. Abumrad NA, Davidson NO. 2012. Role of the gut in lipid homeostasis. *Physiol. Rev.* 92:1061–85
10. Canfora EE, Jocken JW, Blaak EE. 2015. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat. Rev. Endocrinol.* 11:577–91
11. Kosters A, Karpen SJ. 2008. Bile acid transporters in health and disease. *Xenobiotica* 38:1043–71
12. Sarkadi B, Homolya L, Szakács G, Váradi A. 2006. Human multidrug resistance ABCB and ABCG transporters: participation in a chemoimmunity defense system. *Physiol. Rev.* 86:1179–236
13. Jeon T-I, Seo YK, Osborne TF. 2011. Gut bitter taste receptor signalling induces ABCB1 through a mechanism involving CCK. *Biochem. J.* 438:33–37
14. Rehfeld JF. 2004. A centenary of gastrointestinal endocrinology. *Horm. Metab. Res.* 36:735–41
15. Habib AM, Richards P, Cairns LS, Rogers GJ, Bannon CA, et al. 2012. Overlap of endocrine hormone expression in the mouse intestine revealed by transcriptional profiling and flow cytometry. *Endocrinology* 153:3054–65
16. Solcia E, Rindi G, Buffa R, Fiocca R, Capella C. 2000. Gastric endocrine cells: types, function and growth. *Regul. Pept.* 93:31–35
17. Bohórquez DV, Shahid RA, Erdmann A, Kreger AM, Wang Y, et al. 2015. Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. *J. Clin. Investig.* 125:782–86
18. Müller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD, et al. 2015. Ghrelin. *Mol. Metab.* 4:437–60
19. Steinert RE, Beglinger C, Langhans W. 2016. Intestinal GLP-1 and satiation: from man to rodents and back. *Int. J. Obes.* 40:198–205
20. Manning S, Batterham RL. 2014. The role of gut hormone peptide YY in energy and glucose homeostasis: twelve years on. *Annu. Rev. Physiol.* 76:585–608
21. Rehfeld JF. 2017. Cholecystokinin—from local gut hormone to ubiquitous messenger. *Front. Endocrinol.* 8:47
22. Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, et al. 2007. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *PNAS* 104:15069–74
23. Steinert RE, Gerspach AC, Gutmann H, Asarian L, Drewe J, Beglinger C. 2011. The functional involvement of gut-expressed sweet taste receptors in glucose-stimulated secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). *Clin. Nutr.* 30:524–32
24. Margolskee RF, Dyer J, Kokrashvili Z, Salmon KS, Ilegems E, et al. 2007. T1R3 and gustducin in gut sense sugars to regulate expression of Na^+-glucose cotransporter 1. *PNAS* 104:15075–80
25. Gerspach AC, Steinert RE, Schönenberger L, Graber-Maier A, Beglinger C. 2011. The role of the gut sweet taste receptor in regulating GLP-1, PYY, and CCK release in humans. *Am. J. Physiol. Endocrinol. Metab.* 301:E317–25

26. Reimann F, Habib AM, Tolhurst G, Parker HE, Rogers GJ, Gribble FM. 2008. Glucose sensing in L cells: a primary cell study. *Cell Metab.* 8:532–39
27. Parker HE, Adriaenssens A, Rogers G, Richards P, Koepsell H, et al. 2012. Predominant role of active versus facilitative glucose transport for glucagon-like peptide-1 secretion. *Diabetologia* 55:2445–55
28. Gorboulev V, Schürmann A, Vallon V, Kipp H, Jaschke A, et al. 2011. Na^+-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. *Diabetes* 61:187–96
29. Nielsen LB, Ploug KB, Swift P, Ørskov C, Jansen-Olesen I, et al. 2007. Co-localisation of the Kir6.2/SUR1 channel complex with glucagon-like peptide-1 and glucose-dependent insulinotrophic polypeptide expression in human ileal cells and implications for glycaemic control in new onset type 1 diabetes. *Eur. J. Endocrinol.* 156:663–71
30. Reimann F, Gribble FM. 2002. Glucose-sensing in glucagon-like peptide-1-secreting cells. *Diabetes* 51:2757–63
31. Stephens JW, Bodvarsdottir TB, Wareham K, Prior SL, Bracken RM, et al. 2011. Effects of short-term therapy with glibenclamide and repaglinide on incretin hormones and oxidative damage associated with postprandial hyperglycaemia in people with type 2 diabetes mellitus. *Diabetes Res. Clin. Pract.* 94:199–206
32. Steensels S, Vancleef L, Depoortere I. 2016. The sweetener-sensing mechanisms of the ghrelin cell. *Nutrients* 8:795
33. Steensels S, Cools L, Avau B, Vancleef L, Farre R, et al. 2016. Supplementation of oligofructose, but not sucralose, decreases high-fat diet induced body weight gain in mice independent of gustducin-mediated gut hormone release. *Mol. Nutr. Food Res.* 61:1600716
34. Steinert RE, Frey F, Töpfer A, Drewe J, Beglinger C. 2011. Effects of carbohydrate sugars and artificial sweeteners on appetite and the secretion of gastrointestinal satiety peptides. *Br. J. Nutr.* 105:1320–28
35. DuBois GE. 2016. Molecular mechanism of sweetness sensation. *Physiol. Behav.* 164:453–63
36. Engelstoft MS, Park WM, Sakata I, Kristensen LV, Husted AS, et al. 2013. Seven transmembrane G protein-coupled receptor repertoire of gastric ghrelin cells. *Mol. Metab.* 2:376–92
37. Haid DC, Jordan-Biegger C, Widmayer P, Breer H. 2012. Receptors responsive to protein breakdown products in G-cells and D-cells of mouse, swine and human. *Front. Physiol.* 3:65
38. Vancleef L, Van Den Broeck T, Thijs T, Steensels S, Briand L, et al. 2015. Chemosensory signalling pathways involved in sensing of amino acids by the ghrelin cell. *Sci. Rep.* 5:15725
39. Nakajima S, Hira T, Hara H. 2012. Calcium-sensing receptor mediates dietary peptide-induced CCK secretion in enteroendocrine STC-1 cells. *Mol. Nutr. Food Res.* 56:753–60
40. Liou AP, Sei Y, Zhao X, Feng J, Lu X, et al. 2011. The extracellular calcium-sensing receptor is required for cholecystokinin secretion in response to L-phenylalanine in acutely isolated intestinal I cells. *Am. J. Physiol. Gastrointest. Liver Physiol.* 300:G538–46
41. Oya M, Kitaguchi T, Pais R, Reimann F, Gribble F, Tsuboi T. 2013. The G protein-coupled receptor family C group 6 subtype A (GPRC6A) receptor is involved in amino acid-induced glucagon-like peptide-1 secretion from GLUTag cells. *J. Biol. Chem.* 288:4513–21
42. Clemmensen C, Jørgensen CV, Smajilovic S, Brauner-Osborne H. 2016. Robust GLP-1 secretion by basic L-amino acids does not require the GPRC6A receptor. *Diabetes Obes. Metab.* 19:599–603
43. Nelson G, Chandrashekar J, Hoon MA, Feng L, Zhao G, et al. 2002. An amino-acid taste receptor. *Nature* 416:199–202
44. Daly K, Al-Rammahi M, Moran A, Marcello M, Ninomiya Y, Shirazi-Beechey SP. 2013. Sensing of amino acids by the gut-expressed taste receptor T1R1-T1R3 stimulates CCK secretion. *Am. J. Physiol. Gastrointest. Liver Physiol.* 304:G271–82
45. Choi S, Lee M, Shiu AL, Yo SJ, Halldén G, Aponte GW. 2007. GPR93 activation by protein hydrolysate induces CCK transcription and secretion in STC-1 cells. *Am. J. Physiol. Gastrointest. Liver Physiol.* 292:G1366–75
46. Diakogiannaki E, Pais R, Tolhurst G, Parker HE, Horscroft J, et al. 2013. Oligopeptides stimulate glucagon-like peptide-1 secretion in mice through proton-coupled uptake and the calcium-sensing receptor. *Diabetologia* 56:2688–96
47. Pais R, Gribble FM, Reimann F. 2016. Signalling pathways involved in the detection of peptones by murine small intestinal enteroendocrine L-cells. *Peptides* 77:9–15

48. Liou AP, Chavez DI, Espero E, Hao S, Wank SA, Raybould HE. 2011. Protein hydrolysate-induced cholecystokinin secretion from enteroendocrine cells is indirectly mediated by the intestinal oligopeptide transporter PepT1. *Am. J. Physiol. Gastrointest. Liver Physiol.* 300:G895–902
49. Hara T, Kashihara D, Ichimura A, Kimura I, Tsujimoto G, Hirasawa A. 2014. Role of free fatty acid receptors in the regulation of energy metabolism. *Biochim. Biophys. Acta* 1841:1292–300
50. Liou AP, Lu X, Sei Y, Zhao X, Pechhold S, et al. 2011. The G-protein-coupled receptor GPR40 directly mediates long-chain fatty acid-induced secretion of cholecystokinin. *Gastroenterology* 140:903–12
51. Edfalk S, Steneberg P, Edlund H. 2008. *Gpr40* is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. *Diabetes* 57:2280–87
52. Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, et al. 2005. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat. Med.* 11:90–94
53. Janssen S, Laermans J, Iwakura H, Tack J, Depoortere I. 2012. Sensing of fatty acids for octanoylation of ghrelin involves a gustatory G-protein. *PLOS ONE* 7:e40168
54. Sundaresan S, Shahid R, Riehl TE, Chandra R, Nassir F, et al. 2013. CD36-dependent signaling mediates fatty acid-induced gut release of secretin and cholecystokinin. *FASEB J.* 27:1191–202
55. Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, et al. 2012. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* 61:364–71
56. Lin HV, Frassetto A, Kowalik EJ Jr., Nawrocki AR, Lu MM, et al. 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
57. Pluznick J. 2014. A novel SCFA receptor, the microbiota, and blood pressure regulation. *Gut Microbes* 5:202–7
58. Fleischer J, Bumbalo R, Bautze V, Strotmann J, Breer H. 2015. Expression of odorant receptor Olfr78 in enteroendocrine cells of the colon. *Cell Tissue Res.* 361:697–710
59. Overton HA, Fyfe MC, Reynet C. 2008. GPR119, a novel G protein-coupled receptor target for the treatment of type 2 diabetes and obesity. *Br. J. Pharmacol.* 153(Suppl. 1):S76–81
60. Lan H, Vassileva G, Corona A, Liu L, Baker H, et al. 2009. GPR119 is required for physiological regulation of glucagon-like peptide-1 secretion but not for metabolic homeostasis. *J. Endocrinol.* 201:219–30
61. Moss CE, Glass LL, Diakogiannaki E, Pais R, Lenaghan C, et al. 2016. Lipid derivatives activate GPR119 and trigger GLP-1 secretion in primary murine L-cells. *Peptides* 77:16–20
62. Poreba MA, Dong CX, Li SK, Stahl A, Miner JH, Brubaker PL. 2012. Role of fatty acid transport protein 4 in oleic acid-induced glucagon-like peptide-1 secretion from murine intestinal L cells. *Am. J. Physiol. Endocrinol. Metab.* 303:E899–907
63. Van Nierop FS, Scheltema MJ, Eggink HM, Pols TW, Sonne DP, et al. 2017. Clinical relevance of the bile acid receptor TGR5 in metabolism. *Lancet Diabetes Endocrinol.* 5:224–33
64. Brighton CA, Rievaj J, Kuhre RE, Glass LL, Schoonjans K, et al. 2015. Bile acids trigger GLP-1 release predominantly by accessing basolaterally located G protein-coupled bile acid receptors. *Endocrinology* 156:3961–70
65. Trabelsi M-S, Daoudi M, Prawitt J, Ducastel S, Touche V, et al. 2015. Farnesoid X receptor inhibits glucagon-like peptide-1 production by enteroendocrine L cells. *Nat. Commun.* 6:7629
66. Avau B, Depoortere I. 2016. The bitter truth about bitter taste receptors: beyond sensing bitter in the oral cavity. *Acta Physiol.* 216:407–20
67. Rozengurt E. 2006. Taste receptors in the gastrointestinal tract. I. Bitter taste receptors and α-gustducin in the mammalian gut. *Am. J. Physiol. Gastrointest. Liver Physiol.* 291:G171–77
68. Park J, Kim KS, Kim KH, Lee IS, Jeong HS, et al. 2015. GLP-1 secretion is stimulated by 1,10-phenanthroline via colocalized T2R5 signal transduction in human enteroendocrine L cell. *Biochem. Biophys. Res. Commun.* 468:306–11
69. Latorre R, Huynh J, Mazzoni M, Gupta A, Bonora E, et al. 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
70. Kim KS, Egan JM, Jang HJ. 2014. Denatonium induces secretion of glucagon-like peptide-1 through activation of bitter taste receptor pathways. *Diabetologia* 57:2117–25

71. Janssen S, Laermans J, Verhulst PJ, Thijs T, Tack J, Depoortere I. 2011. Bitter taste receptors and α-gustducin regulate the secretion of ghrelin with functional effects on food intake and gastric emptying. *PNAS* 108:2094–99
72. Serrano J, Casanova-Martí À, Depoortere I, Blay MT, Terra X, et al. 2016. Subchronic treatment with grape-seed phenolics inhibits ghrelin production despite a short-term stimulation of ghrelin secretion produced by bitter-sensing flavanols. *Mol. Nutr. Food Res.* 60:2554–64
73. Holzer P. 2011. TRP channels in the digestive system. *Curr. Pharm. Biotechnol.* 12:24–34
74. Nozawa K, Kawabata-Shoda E, Doihara H, Kojima R, Okada H, et al. 2009. TRPA1 regulates gastrointestinal motility through serotonin release from enterochromaffin cells. *PNAS* 106:3408–13
75. Camacho S, Michlig S, de Senarclens-Bezencon C, Meylan J, Meystre J, et al. 2015. Anti-obesity and anti-hyperglycemic effects of cinnamaldehyde via altered ghrelin secretion and functional impact on food intake and gastric emptying. *Sci. Rep.* 5:7919
76. Emery EC, Diakogiannaki E, Gentry C, Psichas A, Habib AM, et al. 2015. Stimulation of GLP-1 secretion downstream of the ligand-gated ion channel TRPA1. *Diabetes* 64:1202–10
77. Purhonen AK, Louhivuori LM, Kiehne K, Kerman KE, Herzig KH. 2008. TRPA1 channel activation induces cholecystokinin release via extracellular calcium. *FEBS Lett.* 582:229–32
78. Kim MJ, Son HJ, Song SH, Jung M, Kim Y, Rhyu MR. 2013. The TRPA1 agonist, methyl syringate suppresses food intake and gastric emptying. *PLOS ONE* 8:e71603
79. van Avesaat M, Troost FJ, Westerterp-Plantenga MS, Helyes Z, Le Roux CW, et al. 2016. Capsaicin-induced satiety is associated with gastrointestinal distress but not with the release of satiety hormones. *Am. J. Clin. Nutr.* 103:305–13
80. Smeets AJ, Westerterp-Plantenga MS. 2009. The acute effects of a lunch containing capsaicin on energy and substrate utilisation, hormones, and satiety. *Eur. J. Nutr.* 48:229–34
81. Braun T, Voland P, Kunz L, Prinz C, Gratzl M. 2007. Enterochromaffin cells of the human gut: sensors for spices and odorants. *Gastroenterology* 132:1890–901
82. Cani PD, Knauf C. 2016. How gut microbes talk to organs: the role of endocrine and nervous routes. *Mol. Metab.* 5:743–52
83. Duca FA, Swartz TD, Sakar Y, Covasa M. 2012. Increased oral detection, but decreased intestinal signaling for fats in mice lacking gut microbiota. *PLOS ONE* 7:e39748
84. Swartz TD, Duca FA, de Wouters T, Sakar Y, 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. *Br. J. Nutr.* 107:621–30
85. Bogunovic M, Davé SH, Tilstra JS, Chang DT, Harpaz N, et al. 2007. Enteroendocrine cells express functional Toll-like receptors. *Am. J. Physiol. Gastrointest. Liver Physiol.* 292:G1770–83
86. Larraufie P, Doré J, Lapaque N, Blottière HM. 2017. TLR ligands and butyrate increase *Pyy* expression through two distinct but inter-regulated pathways. *Cell. Microbiol.* 19:e12648
87. Sonnenburg JL, Backhed F. 2016. Diet-microbiota interactions as moderators of human metabolism. *Nature* 535:56–64
88. Brookes SJ, Spencer NJ, Costa M, Zagorodnyuk VP. 2013. Extrinsic primary afferent signalling in the gut. *Nat. Rev. Gastroenterol. Hepatol.* 10:286–96
89. Bertrand PP, Kunze WA, Bornstein JC, Furness JB, Smith ML. 1997. Analysis of the responses of myenteric neurons in the small intestine to chemical stimulation of the mucosa. *Am. J. Physiol.* 273:G422–35
90. Liu M, Seino S, Kirchgessner AL. 1999. Identification and characterization of glucoresponsive neurons in the enteric nervous system. *J. Neurosci.* 19:10305–17
91. Diez-Sampedro A, Hirayama BA, Osswald C, Gorboulev V, Baumgarten K, et al. 2003. A glucose sensor hiding in a family of transporters. *PNAS* 100:11753–58
92. Rühl A, Hoppe S, Frey I, Daniel H, Schemann M. 2005. Functional expression of the peptide transporter PEPT2 in the mammalian enteric nervous system. *J. Comp. Neurol.* 490:1–11
93. Nøhr MK, Pedersen MH, Gille A, Egerod KL, Engelstoft MS, et al. 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* 154:3552–64

94. Soret R, Chevalier J, De Coppet P, Poupeau G, Derkinderen P, et al. 2010. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. *Gastroenterology* 138:1772–82
95. Page AJ, Symonds E, Peiris M, Blackshaw LA, Young RL. 2012. Peripheral neural targets in obesity. *Br. J. Pharmacol.* 166:1537–58
96. Williams EK, Chang RB, Strochlic DE, Umans BD, Lowell BB, Liberles SD. 2016. Sensory neurons that detect stretch and nutrients in the digestive system. *Cell* 166:209–21
97. Zhang Y, Hoon MA, Chandrashekar J, Mueller KL, Cook B, et al. 2003. Coding of sweet, bitter, and umami tastes: different receptor cells sharing similar signaling pathways. *Cell* 112:293–301
98. Yu X, Yu M, Liu Y, Yu S. 2016. TRP channel functions in the gastrointestinal tract. *Semin. Immunopathol.* 38:385–96
99. Buckinx R, Van Nassauw L, Avula LR, Alpaerts K, Adriaensen D, Timmermans JP. 2013. Transient receptor potential vanilloid type 1 channel (TRPV1) immunolocalization in the murine enteric nervous system is affected by the targeted C-terminal epitope of the applied antibody. *J. Histochem. Cytochem.* 61:421–32
100. Liu XJ, Liu T, Chen G, Wang B, Yu XL, et al. 2016. TLR signaling adaptor protein MyD88 in primary sensory neurons contributes to persistent inflammatory and neuropathic pain and neuroinflammation. *Sci. Rep.* 6:28188
101. Burgueño JF, Barba A, Eyre E, Romero C, Neunlist M, Fernández E. 2016. TLR2 and TLR9 modulate enteric nervous system inflammatory responses to lipopolysaccharide. *J. Neuroinflamm.* 13:187
102. Höfer D, Püschel B, Drenckhahn D. 1996. Taste receptor-like cells in the rat gut identified by expression of α-gustducin. *PNAS* 93:6631–34
103. Hass N, Schwarzenbacher K, Breer H. 2007. A cluster of gustducin-expressing cells in the mouse stomach associated with two distinct populations of enteroendocrine cells. *Histochem. Cell Biol.* 128:457–71
104. Hass N, Schwarzenbacher K, Breer H. 2010. T1R3 is expressed in brush cells and ghrelin-producing cells of murine stomach. *Cell Tissue Res.* 339:493–504
105. Eberle JAM, Richter P, Widmayer P, Chubanov V, Gudermann T, Breer H. 2013. Band-like arrangement of taste-like sensory cells at the gastric groove: evidence for paracrine communication. *Front. Physiol.* 4:58
106. Eberle JAM, Widmayer P, Breer H. 2014. Receptors for short-chain fatty acids in brush cells at the "gastric groove." *Front. Physiol.* 5:152
107. Bezençon C, le Coutre J, Damak S. 2007. Taste-signaling proteins are coexpressed in solitary intestinal epithelial cells. *Chem. Senses* 32:41–49
108. Schütz B, Jurastow I, Bader S, Ringer C, von Engelhardt J, et al. 2015. Chemical coding and chemosensory properties of cholinergic brush cells in the mouse gastrointestinal and biliary tract. *Front. Physiol.* 6:87
109. Gerbe F, Sidot E, Smyth DJ, Ohmoto M, Matsumoto I, et al. 2016. Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. *Nature* 529:226–30
110. Howitt MR, Lavoie S, Michaud M, Blum AM, Tran SV, et al. 2016. Tuft cells, taste-chemosensory cells, orchestrate parasite type 2 immunity in the gut. *Science* 351:1329–33
111. von Moltke J, Ji M, Liang HE, Locksley RM. 2016. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* 529:221–25
112. Zhao A, Urban JF Jr., Anthony RM, Sun R, Stiltz J, et al. 2008. Th2 cytokine-induced alterations in intestinal smooth muscle function depend on alternatively activated macrophages. *Gastroenterology* 135:217–25.e1
113. Gersemann M, Wehkamp J, Stange EF. 2012. Innate immune dysfunction in inflammatory bowel disease. *J. Intern. Med.* 271:421–28
114. Johansson MEV, Hansson GC. 2016. Immunological aspects of intestinal mucus and mucins. *Nat. Rev. Immunol.* 16:639–49
115. Ganz T. 2003. Defensins: antimicrobial peptides of innate immunity. *Nat. Rev. Immunol.* 3:710–20
116. Mace OJ, Affleck J, Patel N, Kellett GL. 2007. Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. *J. Physiol.* 582:379–92
117. Prandi S, Bromke M, Hübner S, Voigt A, Boehm U, et al. 2013. A subset of mouse colonic goblet cells expresses the bitter taste receptor Tas2r131. *PLOS ONE* 8:e82820

118. Lee RJ, Kofonow JM, Rosen PL, Siebert AP, Chen B, et al. 2014. Bitter and sweet taste receptors regulate human upper respiratory innate immunity. *J. Clin. Investig.* 124:1393–405
119. Ayabe T, Satchell DP, Wilson CL, Parks WC, Selsted ME, Ouellette AJ. 2000. Secretion of microbicidal α-defensins by intestinal Paneth cells in response to bacteria. *Nat. Immunol.* 1:113–18
120. Lala S, Ogura Y, Osborne C, Hor SY, Bromfield A, et al. 2003. Crohn's disease and the NOD2 gene: a role for Paneth cells. *Gastroenterology* 125:47–57
121. Clevers HC, Bevins CL. 2013. Paneth cells: maestros of the small intestinal crypts. *Annu. Rev. Physiol.* 75:289–311
122. Maliphol AB, Garth DJ, Medler KF. 2013. Diet-induced obesity reduces the responsiveness of the peripheral taste receptor cells. *PLOS ONE* 8:e79403
123. Chevrot M, Bernard A, Ancel D, Buttet M, Martin C, et al. 2013. Obesity alters the gustatory perception of lipids in the mouse: plausible involvement of lingual CD36. *J. Lipid Res.* 54:2485–94
124. Stewart JE, Seimon RV, Otto B, Keast RS, Clifton PM, Feinle-Bisset C. 2011. Marked differences in gustatory and gastrointestinal sensitivity to oleic acid between lean and obese men. *Am. J. Clin. Nutr.* 93:703–11
125. Bartoshuk LM, Duffy VB, Hayes JE, Moskowitz HR, Snyder DJ. 2006. Psychophysics of sweet and fat perception in obesity: problems, solutions and new perspectives. *Philos. Trans. R. Soc. B* 361:1137–48
126. Scholtz S, Miras AD, Chhina N, Prechtl CG, Sleeth ML, et al. 2014. Obese patients after gastric bypass surgery have lower brain-hedonic responses to food than after gastric banding. *Gut* 63:891–902
127. Little TJ, Isaacs NJ, Young RL, Ott R, Nguyen NQ, et al. 2014. Characterization of duodenal expression and localization of fatty acid-sensing receptors in humans: relationships with body mass index. *Am. J. Physiol. Gastrointest. Liver Physiol.* 307:G958–67
128. Heni M, Müssig K, Machicao F, Machann J, Schick F, et al. 2011. Variants in the *CD36* gene locus determine whole-body adiposity, but have no independent effect on insulin sensitivity. *Obesity* 19:1004–9
129. Chambers ES, Viardot A, Psichas A, Morrison DJ, Murphy KG, et al. 2015. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. *Gut* 64:1744–54
130. van der Beek CM, Canfora EE, Lenaerts K, Troost FJ, Damink SW, et al. 2016. Distal, not proximal, colonic acetate infusions promote fat oxidation and improve metabolic markers in overweight/obese men. *Clin. Sci.* 130:2073–82
131. Dotson CD, Shaw HL, Mitchell BD, Munger SD, Steinle NI. 2010. Variation in the gene *TAS2R38* is associated with the eating behavior disinhibition in Old Order Amish women. *Appetite* 54:93–99
132. Vegezzi G, Anselmi L, Huynh J, Barocelli E, Rozengurt E, et al. 2014. Diet-induced regulation of bitter taste receptor subtypes in the mouse gastrointestinal tract. *PLOS ONE* 9:e107732
133. Avau B, Bauters D, Steensels S, Vancleef L, Laermans J, et al. 2015. The gustatory signaling pathway and bitter taste receptors affect the development of obesity and adipocyte metabolism in mice. *PLOS ONE* 10:e0145538
134. Avau B, Rotondo A, Thijs T, Andrews CN, Janssen P, et al. 2015. Targeting extra-oral bitter taste receptors modulates gastrointestinal motility with effects on satiation. *Sci. Rep.* 5:15985
135. Deloose E, Janssen P, Corsetti M, Biesiekierski J, Masuy I, et al. 2017. Intragastric infusion of denatonium benzoate attenuates interdigestive gastric motility and hunger scores in healthy female volunteers. *Am. J. Clin. Nutr.* 105:580–88
136. Fushan AA, Simons CT, Slack JP, Drayna D. 2010. Association between common variation in genes encoding sweet taste signaling components and human sucrose perception. *Chem. Senses* 35:579–92
137. Fushan AA, Simons CT, Slack JP, Manichaikul A, Drayna D. 2009. Allelic polymorphism within the *TAS1R3* promoter is associated with human taste sensitivity to sucrose. *Curr. Biol.* 19:1288–93
138. Young RL, Chia B, Isaacs NJ, Ma J, Khoo J, et al. 2013. Disordered control of intestinal sweet taste receptor expression and glucose absorption in type 2 diabetes. *Diabetes* 62:3532–41
139. Nguyen NQ, Debreceni TL, Bambrick JE, Chia B, Wishart J, et al. 2015. Accelerated intestinal glucose absorption in morbidly obese humans: relationship to glucose transporters, incretin hormones, and glycemia. *J. Clin. Endocrinol. Metab.* 100:968–76

140. Rosenstock J, Hansen L, Zee P, Li Y, Cook W, et al. 2015. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care* 38:376–83
141. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, et al. 2014. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* 514:181–86
142. de Ruyter JC, Olthof MR, Seidell JC, Katan MB. 2012. A trial of sugar-free or sugar-sweetened beverages and body weight in children. *N. Engl. J. Med.* 367:1397–406
143. Tate DF, Turner-McGrievy G, Lyons E, Stevens J, Erickson K, et al. 2012. Replacing caloric beverages with water or diet beverages for weight loss in adults: main results of the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial. *Am. J. Clin. Nutr.* 95:555–63
144. Mancini AD, Poitout V. 2015. GPR40 agonists for the treatment of type 2 diabetes: life after 'TAKing' a hit. *Diabetes Obes. Metab.* 17:622–29
145. Steneberg P, Rubins N, Bartoov-Shifman R, Walker MD, Edlund H. 2005. The FFA receptor GPR40 links hyperinsulinemia, hepatic steatosis, and impaired glucose homeostasis in mouse. *Cell Metab.* 1:245–58
146. Oh DY, Olefsky JM. 2016. G protein-coupled receptors as targets for anti-diabetic therapeutics. *Nat. Rev. Drug Discov.* 15:161–72
147. Ichimura A, Hirasawa A, Poulain-Godefroy O, Bonnefond A, Hara T, et al. 2012. Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human. *Nature* 483:350–54
148. Lamri A, Bonnefond A, Meyre D, Balkau B, Roussel R, et al. 2016. Interaction between *GPR120* p.R270H loss-of-function variant and dietary fat intake on incident type 2 diabetes risk in the D.E.S.I.R. study. *Nutr. Metab. Cardiovasc. Dis.* 26:931–36
149. Hansen HS, Rosenkilde MM, Holst JJ, Schwartz TW. 2012. GPR119 as a fat sensor. *Trends Endocrinol. Metab.* 33:374–81
150. Qu D, Weygant N, May R, Chandrakesan P, Madhoun M, et al. 2015. Ablation of doublecortin-like kinase 1 in the colonic epithelium exacerbates dextran sulfate sodium-induced colitis. *PLOS ONE* 10:e0134212
151. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, et al. 2009. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* 461:1282–86
152. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, et al. 2013. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 504:451–55
153. Wang J, Wu X, Simonavicius N, Tian H, Ling L. 2006. Medium-chain fatty acids as ligands for orphan G protein-coupled receptor GPR84. *J. Biol. Chem.* 281:34457–64
154. Guo C, Qi H, Yu Y, Zhang Q, Su J, et al. 2015. The G-protein-coupled bile acid receptor Gpbar1 (TGR5) inhibits gastric inflammation through antagonizing NF-κβ signaling pathway. *Front. Pharmacol.* 6:287