Sensing of nutrients by chemosensory cells in the gastrointestinal tract plays a key role in transmitting food-related signals, linking information about the composition of ingested foods to digestive processes. In recent years, a number of G protein-coupled receptors (GPCR) responsive to a range of nutrients have been identified. Many are localised to intestinal enteroendocrine (chemosensory) cells, promoting hormonal and neuronal signalling locally, centrally and to the periphery. The field of gut sensory systems is relatively new and still evolving. Despite huge interest in these nutrient-sensing GPCR, both as sensors for nutritional status and targets for preventing the development of metabolic diseases, major challenges remain to be resolved. However, the gut expressed sweet taste receptor, resident in L-enteroendocrine cells and responsive to dietary sweetener additives, has already been successfully explored and utilised as a therapeutic target, treating weaning-related disorders in young animals. In addition to sensing nutrients, many GPCR are targets for drugs used in clinical practice. As such these receptors, in particular those expressed in L-cells, are currently being assessed as potential new pathways for treating diabetes and obesity. Furthermore, growing recognition of gut chemosensing of microbial-produced SCFA acids has led further attention to the association between nutrition and development of chronic disorders focusing on the relationship between nutrients, gut microbiota and health. The central importance of gut nutrient sensing in the control of gastrointestinal physiology, health promotion and gut–brain communication offers promise that further therapeutic successes and nutritional recommendations will arise from research in this area.

**Nutrient sensing: Enteroendocrine cell: G protein-coupled receptors**

The intestinal epithelium is a major boundary with the outside world. Epithelial cells lining the surface of the intestinal epithelium are in direct contact with a luminal environment, the composition of which varies dramatically. It has long been recognised that the gut is capable of sensing changes in its luminal content and responding by releasing chemical signals. In 1902, Bayliss and Starling noted that increasing the acidity in the lumen of the small intestine elicited pancreatic secretions, and that this was mediated, not via the nervous system, but by a humoral factor produced by the gut epithelium that they termed secretin.

Abbreviations: cAMP, cyclic adenosine monophosphate; CaSR, calcium-sensing receptor; CCK, cholecystokinin; EEC, enteroendocrine cell; GI, gastrointestinal; GIP, glucose-dependent insulinotropic peptide; GLP, glucagon-like peptide; GPCR, G protein-coupled receptors; PYY, peptide YY; SGLT1, sodium glucose co-transporter isofrom 1; STC1, secretin tumour cell line; T1R, taste 1 family receptor.

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内容不触及肠道内容物的化学性质和这些内容物被传送到神经元的胰岛细胞分泌（EEC）连接到消化道、大脑和周围组织。

EEC，分布在整个消化道的上皮细胞中，是化学感受性途径的起始点。它们呈杆状，与上皮细胞的外表面接触，由具有特定功能的细胞组成，包括产生和分泌胰岛素在内的多种激素，以及微生物产品，这些都在肠道中。这些细胞在生理因素影响下会改变其功能，通过释放进入到循环中，通过基侧膜直接接触摄入的营养素和微生物产品。

**G protein-coupled receptors and intestinal nutrient sensing**

G蛋白偶联受体（GPCR）是最大的细胞表面信号转导器家族。它们由大约800个不同的基因编码，在人类中，这些基因通过不同的组合来编码细胞对不同信号的感知。因此，GPCR是已知的细胞表面受体，由能够感知信号的某些特定信号蛋白进行识别。这些信号蛋白在生理情况下，在细胞内被识别，从而激活细胞内 Websites, Java applets, Flash animations, and JavaScript code can be resized and moved.
are fermented by gut microbiota, predominantly to SCFA.

**Intestinal glucose (sweet) sensing**

Glucose is an effective inducer of secretion of gut hormones such as GLP-1, GLP-2 and glucose-dependent insulinotropic peptide (GIP). It has been shown that there is a much greater insulin secretion from the pancreas after orally-ingested glucose than from intravenous injection of the same amount of glucose (the incretin effect)\(^{14}\), inferring the presence of an intestinal luminal glucose sensor responsible for glucose-induced gut peptide release.

In 2005, we reported, for the first time, that the heterodimeric sweet taste receptor T1R2-T1R3, previously characterised in the lingual epithelium, is expressed in gut EEC, and proposed that it acts as the intestinal glucose sensor\(^{15}\).

Further work demonstrated that all signalling elements involved in sweet taste transduction in the gustatory buds of the tongue, T1R2-T1R3, phospholipase C-β2, transient receptor potential channel M5, α-gustducin and other associated signalling elements, are co-expressed in both L- and K-EEC in human and mouse intestine\(^{16,17}\). In mice in which the genes encoding for α-gustducin and T1R3 were deleted, there was a failure to secrete GLP-1 in response to luminal glucose\(^{16,17}\). These knockout mice also had abnormal insulin response and prolonged elevation of postprandial blood glucose, indicating that the sweet receptor expressed in intestinal L-cells coupled to α-gustducin sense luminal glucose leading to the secretion of GLP-1\(^{16,17}\). More recent work\(^{19}\) has confirmed and extended these studies to demonstrate that in mouse small intestine, T1R2, T1R3, α-gustducin and GLP-2 are co-expressed in the same L-EEC and that mouse intestine secretes GLP-2 in response to glucose\(^{19}\). Moreover, this glucose-induced GLP-2 release was inhibited by gurmarin (a specific inhibitor of mouse T1R3)\(^{20,21}\). Furthermore, the non-nutritive sweetener, sucralose, also induced GLP-2 release from mouse...
small intestine, which was again inhibited by gurmarin. However, the sweetener aspartame, which does not activate mouse T1R2-T1R3(22), did not induce GLP-2 release, supporting the conclusion that the T1R2-T1R3 receptor, expressed in L-cells, senses luminal glucose and sweeteners to secrete GLP-2. A number of studies(3,23,24) confirming the findings of previous reports(16,17) have demonstrated that transcripts for T1R2, T1R3, α-gustducin, transient receptor potential channel M5 and GLP-1 are expressed in the mucosa of the human proximal intestine. Young et al.(23) also reported that the expression of T1R2, at mRNA level, was reduced in the intestine of diabetic subjects with higher fasting blood glucose concentration(23).

The magnitude of GLP-1, GLP-2 and GIP secretion has been reported to be diminished in patients with type 2 diabetes(25). A recent study has also shown that the number of EEC, including L-cells, is reduced significantly in the intestine of morbidly obese and diabetic individuals with type 2 diabetes compared to that in healthy controls(46). Thus, the reduction in T1R2 transcript level observed in diabetics(23) may be due to a reduced number of EEC expressing T1R2 and other signalling elements required for glucose-induced GLP-1 secretion. Moreover, it has been demonstrated that the intragastric administration of glucose, in healthy subjects, resulted in the secretion of GLP-1 and PYY, which was significantly reduced when lactisole, the specific inhibitor of human T1R3(26) was co-administered(3,24). They have concluded that in the human intestine, T1R2-T1R3 is involved in glucose-induced secretion of GLP-1 and PYY, with potential consequences for reducing food intake, decreasing gut motility and increasing insulin secretion (the latter in response to GLP1).

Mechanisms underlying intestinal sweet sensing and glucose transport regulation

One important manifestation of intestinal glucose sensing by T1R2-T1R3, expressed in L-cells, is the regulation of intestinal glucose transport.

The major route for transport of dietary glucose from the lumen of the intestine into absorptive enterocytes is via the brush border membrane protein, the sodium glucose co-transporter isoform 1 (SGLT1)(37,26). Absorption of glucose by SGLT1 also activates electrolyte (NaCl) and water absorption, the route used for oral rehydration therapy(29–31). SGLT1 activity and expression have been shown to be directly regulated by luminal glucose, including metabolisable, non-metabolisable and membrane-impermeable glucose analogues(32–34). Furthermore, the pathway underlying monosaccharide-enhanced SGLT1 expression was via a luminal membrane glucose GPCR(34,35).

Recent experimental evidence has demonstrated that T1R2-T1R3 expressed in L-cells senses dietary glucose (and other natural/artificial sweeteners) resulting in the secretion of GLP-2, which then, via a neuro-paracrine pathway involving the enteric nervous system, enhances the half-life of SGLT1 mRNA in neighbouring absorptive enterocytes. This leads to increased activity and expression of SGLT1, and enhanced intestinal glucose absorption(19). Knocking out the genes for T1R2, T1R3 or GLP-2 receptor abolishes the ability of mouse intestine to up-regulate SGLT1 expression and activity in response to luminal glucose or sweeteners(17,19).

It has been shown that the expression (and activity) of SGLT1 is enhanced in the intestine of human subjects with type 2 diabetes. This increase was shown to be independent of dietary carbohydrate intake level, or any changes in blood glucose or insulin concentrations(27), and proposed to be due to alterations in the mechanisms and signalling pathways involved in the regulation of SGLT1 activity and expression.

As noted earlier, the total number of EEC, the expression of T1R2 and levels of gut hormones including GLP-1, GLP-2 and GIP are all significantly reduced in the intestine of diabetic individuals(4,23,25). Thus, it appears that in type 2 diabetes, deregulation of intestinal glucose sensing and downstream signalling may play a role in the observed overexpression of intestinal SGLT1.

Therapeutic potential of taste 1 receptor 2 and receptor 3

Post weaning intestinal disorders are major health problems for the young. Weaning-associated diarrhoea, dehydration and nutrient malabsorption result in high levels of mortality in farm animals worldwide. The finding that small concentrations of specific natural/artificial sweeteners are detected by the intestinal T1R2-T1R3 sweet receptor, activating the pathway leading to increased glucose, electrolyte and water absorption (oral rehydration therapy)(29) has attracted worldwide uptake of these additive sweeteners in the diet of weaning animals. This innovation has improved the health and survival rate of young animals through avoidance of intestinal disorders, thereby increasing weight, enhancing immunity and optimising feed utilisation allowing the translation of scientific discoveries to animal health and welfare benefits(3,31,36,37). Modulation of human intestinal T1R2-T1R3 activity may also have applications in human subjects by controlling glucose absorption(23).

Proteins

Dietary proteins are essential for growth, provision of energy and health maintenance. In the small intestine, proteins are digested by pancreatic and brush border membrane proteases to di-tri-oligopeptides and amino acids. There are these products that likely target EEC, including CCK, GLP-1 and PYY(38). The satiety effects associated with high-protein diets can also be mediated by sensing of the amino acid constituents of proteins.

Intestinal sensing of protein hydrolysate products

Amino acid sensing

A number of GPCR have been identified to respond to amino acids. They belong to a sub-group of C class GPCR and include CaSR, the heterodimeric umami
receptor T1R1-T1R3, the goldfish 5-24 receptor and its mammalian orthologue GPCR6A, and the metabolotropic glutamate receptors.

CaSR is a homodimeric receptor that predominantly couples to G\textsubscript{q\alpha} activating phosphatidylinositol-specific phospholipase C and inducing mobilisation of intracellular Ca\textsuperscript{2+}(39). However, it also couples to G\textsubscript{i\alpha} and G\textsubscript{12/13}. CaSR is a multimodal sensor for several key nutrients, notably Ca\textsuperscript{2+} ions and l-amino acids, and is expressed abundantly throughout the GI tract(39,41). Although it acts as a sensor for Ca\textsuperscript{2+} in the gut lumen, it is allosterically activated by l-amino acids; responding to aromatic, aliphatic and polar, but not to branched or positively charged, amino acids(42). CaSR is highly expressed in gastrin-secreting G- and somatostatin-secreting D-(43) and CCK-secreting I-cells(44), and has been proposed to facilitate amino acid-induced secretion of these gut hormones. In studies using secretin tumour cell line (STC)-1 cells, it was shown that extracellular presence of l-phenylalanine induced mobilisation of intracellular Ca\textsuperscript{2+} and CCK secretion which was inhibited with the allosteric CaSR inhibitor NPS2143(45). Moreover, native intestinal I-cells from mice deficient in CaSR showed impaired l-phenylalanine mediated Ca\textsuperscript{2+} responses and CCK release(44), indicating that CaSR plays a significant role in the chemosensing of amino acids in the GI tract.

GPCR6A is a G\textsubscript{q\alpha} coupled receptor widely expressed in human and rodent tissues. Being a promiscuous amino acid sensor, and expressed in the digestive system, it has been proposed to act as a candidate for sensing digested amino acids in the GI tract(43,46). It has been reported by two groups that GPCR6A is involved in l-ornithine-induced GLP-1 release in the intestinal L-cell line GLUTag(47,48). However, Oya \textit{et al.}(48) were unable to measure l-ornithine-induced GLP-1 release from mixed primary cultures of mouse small intestine(48). There are equally conflicting results using GPCR6A knockout mouse models. Alamshah \textit{et al.}(49) demonstrated that l-arginine induced secretion of PYY from both wild-type and GPCR6A KO mouse primary colonic L-cells(49). Jørgensen & Bräuner-Osborne (50) addressing the in \textit{vivo} relevance of these findings, administered l-ornithine and l-arginine orally to the full locus and exon VI GPCR6A KO mouse models(50). Whilst there was an immediate GLP-1 release that diminished over time, there were no overall differences in the ability of KO-mouse models and wild-type mice to secrete GLP-1 in response to these amino acids. The authors concluded that GPCR6A, in \textit{vivo}, does not play a role in GLP-1 secretion in response to basic l-amino acids(50). Further work is required to unravel the precise role of GPCR6A in intestinal chemosensing.

\textbf{Taste 1 receptor 1 and receptor 3}

In taste cells of lingual epithelium, the heterodimeric combination of T1R1 and T1R3, members of the T1R family, has been identified as a broad-spectrum l-amino acid sensor responsible for mediating perception of the savoury umami taste of monosodium glutamate(22,51). In rodents and many other mammalian species, T1R1-T1R3 responds to a wide variety of l-amino acids in the millimolar range. However, the receptor is not activated by l-tryptophan(10). The human T1R1-T1R3 complex functions as a much more specific receptor, responding selectively to monosodium glutamate and aspartic acid (as well as to the glutamate analogue l-AP4)(22,51,52). The T1R1-T1R3 heterodimer, such as the sweet receptor T1R2-T1R3, is expressed in EEC(15) and is coupled to gustducin for the transmission of intracellular signals(53). Using STC-1 cells and native mouse intestinal tissue, it has been shown that gut expressed T1R1-T1R3 serves as an intestinal l-amino acid sensor modulating amino acid-induced CCK release(54). Using siRNA to inhibit the expression of T1R1 mRNA and protein in STC-1 cells, it was demonstrated that the inhibition of T1R1 expression had no effect on protein hydrolysate or peptide-induced CCK release, indicating that T1R1-T1R3 is not the intestinal sensor for peptones. However, in T1R1 knockdown STC-1 cells, there was a significant decline in phenylalanine-, leucine- and glutamate-induced CCK release. Conversely, tryptophan-induced CCK secretion was unaffected by inhibition of T1R1 expression, in agreement with tryptophan not being an agonist for T1R1-T1R3(54).

Thus, both CaSR and T1R1-T1R3 have been recognised as intestinal l-amino acid sensors mediating CCK secretion in response to aromatic amino acids such as l-phenylalanine(44,54). Using a range of agonists and antagonists of CaSR and T1R1-T1R3, it has been demonstrated that CaSR is an intestinal l-amino acid receptor specifically sensing aromatic amino acids, while T1R1-T1R3 responds to a broad spectrum of l-amino acids provoking CCK secretion from intestinal endocrine I-cells(54).

\textbf{Peptone receptor}

The identity of the cell surface receptor(s) involved in peptone-induced CCK release remains unknown. GPCR92/93 is not a member of the C-class GPCR but has been proposed as a candidate sensor for peptones in STC-1 cells(55). Further work is required to elucidate the peptone-sensing role of this GPCR, if any, in the intestine.

\textbf{Fats}

Fats play an important role in nutrition. As well as providing 30–40% of total body energy, they also offer essential fatty acids such as linoleic (n-6) and α-linoleic (n-3) acid that cannot be \textit{de novo} synthesised in the body. Like other macronutrients, fats must first be digested before triggering hormone secretion and are much more effective when administered into the gut lumen than into the circulation. Fat ingestion stimulates the secretion of a number of gut hormones, including CCK, GLP-1 and GIP(56). It is reported that long-chain fatty acids inhibit gastric emptying and induce satiety(57), with SCFA eliciting GLP-1 and PYY secretion(58).
**Intestinal fatty acid sensing**

There are four principal GPCR, FFA1-FFA4, that have been officially classified as members of a NEFA receptor family. FFA1 (GPR40) and FFA4 (GPR120) are activated by both saturated and unsaturated medium-chain (carbon length 8–12) and longer chain (carbon chain length 14–22) fatty acids and are mainly $G_{aq}$-coupled \(^{(59)}\). The supporting evidence that long-chain fatty acid receptors contribute directly to intestinal fatty acid chemosensing is from the findings that their expression in the GI tract is largely limited to the EEC population. The pattern of expression of FFA4 in EEC appears to be similar to that of FFA1. This has highlighted the need for highly selective ligands to probe their functions. A number of preclinical and clinical development programmes have explored the therapeutic potential of agonists of FFA1 \(^{(60,61)}\). Indeed, some synthetic agonists of FFA1 have shown the capacity to improve glycaemic control in diabetes \(^{(62)}\). However, questions remain in terms of sustainability of effects during long-term treatment. There are conflicting experimental evidence relating to the roles of FFA1 and FFA4 and is not clear which one plays a more important role in enteronecocrine fatty acid sensing \(^{(63)}\). Despite such concerns, the evidence suggests many positive reasons to promote FFA4 as a promising therapeutic target. They include the potential capacity to regulate GLP-1 secretion from L-cells to promote insulin release and to reduce insulin resistance via anti-inflammatory mechanisms. Thus, efforts have been made in medicinal chemistry for improving the selectivity of ligands between FFA1 and FFA4, and it is proposed that perhaps combined agonists of FFA1 and FFA4 may impart greater anti-diabetic efficacy, than targeting either receptor selectively \(^{(64)}\).

The SCFA receptors FFA2 (GPR43) and FFA3 (GPR41) have been shown, by immunohistochemistry, to be expressed in colonic L-cells. They selectively bind to and are activated by SCFA (carbon chain length 1–6), particularly acetate (C\(_2\)), propionate (C\(_3\)) and butyrate (C\(_4\)). FFA2 responds to C\(_2\)–C\(_5\) fatty acids and couples to $G_{aq}$ as well as $G_{i/o}$ whereas FFA3 preferentially binds C\(_3\)–C\(_5\) and couples only to $G_{i/o}$. These SCFA are generated predominantly in the distal gut by microbial fermentation of non-digestible carbohydrates, such as fibre and NSP. It has been reported that non-digestible and fermentable dietary fibre and starch, as well as SCFA themselves, enhance GLP-1 secretion \(^{(65)}\). Moreover, the SCFA-induced release of GLP-1 from EEC appears to be mediated by FFA2 \(^{(66)}\).

Although also activated by the same group of SCFA as FFA2, and with a broadly similar expression profile, FFA3 is less well characterised than FFA2. To date, there have been no reports of highly selective synthetic ligands for FFA3 that target the same binding site as SCFA, and as such, detailed understanding of the function of this receptor lags behind \(^{(67)}\). There is also significant species orthologue variation in the pharmacology of SCFA receptors in respect to their endogenous ligands, which can be translated to species selectivity of synthetic ligands targeting these receptors.

As alterations in population and diversity of gut microbiota are associated with dysbiosis, there is considerable interest in both prebiotic and probiotic strategies to modulate microbial populations and hence the effectiveness of SCFA production \(^{(68)}\). Thus, the physiological role of SCFA receptors, and their relative importance, compared with other possible targets of prebiotic supplementation remains to be established.

**Other NEFA-related receptors**

GPR84 is recognised as a receptor responsive to medium-chain fatty acids. However, it is by far the least studied and understood of the currently described receptors for fatty acids. GPR119 is predominantly coupled to $G_{iq}$ and is responsive to monoacylglycerols, products of TAG hydrolysis. It is proposed that small-molecule ligands of GPR119 increase GLP-1, GIP and insulin release \(^{(69)}\), however studies have shown these ligands have limited glucose lowering and incretin activity in subjects with type 2 diabetes \(^{(70)}\).

**Conclusion**

The nutrient-sensing GPCR, expressed in EEC, play important roles in sensing the gut luminal environment, transmitting nutrient-evoked signals leading to coordination of various physiological functions such as nutrient digestion, absorption, insulin secretion and food intake. Targeting the gut-expressed sweet receptor, T1R2-T1R3, with dietary sweetener additives has made a significant contribution to veterinary medicine, through enhancing absorption of glucose, electrolytes and water (oral rehydration therapy) in young animals, thereby preventing weaning-induced intestinal disorders. This strategy may also have applications for the prevention of digestive disorders in premature or newborn human infants. As many GPCR are targets for numerous drugs used in clinical practice, a number of GPCR expressed in gut chemosensory cells are currently under assessment as potential new pathways for treating diabetes and obesity. However, a number of these receptors remain poorly or incompletely characterised. It is envisaged that access to high-quality and well-defined agonists/antagonists, appropriate animal models, closer collaborations between different disciplines and true ligand selectivity/specificity will allow further expansion of this GPCR repertoire. It is predicted that with these basic criteria in place, the potential for much more convincing target validation of nutrient-sensing GPCR will be possible.

With the major role that gut nutrient sensing plays in the control of GI physiology and gut–brain communication, it is expected that further therapeutic successes and nutritional recommendations will arise from research in this area.

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Conflict of Interest

None.

Authorship

The authors had joint responsibility for preparation of this paper.

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