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Nutrient sensing of gut luminal environment

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Nutrient sensing of gut luminal environment

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Abstract:

Sensing of nutrients by chemosensory cells in the gastrointestinal tract plays a key role in transmitting food related signals, linking information about 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 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 short chain fatty 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.

Introduction

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[1] 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'.

Indeed, we now know that the nerve endings that transmit signals evoked by changes in the gut luminal contents do not reach the intestinal lumen and that information about the chemical nature of the luminal contents is transmitted to neurons via enteroendocrine cells linking the gut, brain and peripheral tissues.

Enteroendocrine cells (EEC), scattered amongst the cells lining the intestinal epithelium are pivotal to the chemosensing pathways of the intestinal tract. They are flask-shaped, with the majority having open-type morphology with apically extended processes making direct contact with ingested nutrients and microbial products in the gut lumen. These cells respond to changes in luminal contents by releasing gut hormones into systemic circulation via their basolateral membrane domain. There are at least sixteen discrete cell types that make up the enteroendocrine family (generally named after letters of alphabet) and collectively they produce over twenty different hormones[2]. These include cholecystokinin (CCK), peptide YY (PYY) and glucagon-like peptides 1 and 2 (GLP-1, GLP-2). CCK is released by I-cells predominantly located in the proximal intestine, whereas PYY, GLP-1 and GLP-2 are secreted mostly by L-cells residing frequently in the distal gut. However, L-cells have also been identified in the duodenum albeit in lower number than observed in jejunum and ileum[3]. Secretion of CCK, GLP-1 or PYY slows down gastric emptying, as well as reducing appetite and food intake. GLP-1 also functions as an incretin hormone, stimulating insulin secretion from pancreatic β-cells, improving meal-related glycaemia. GLP-2, coproduced with GLP-1, promotes intestinal epithelial cell growth and increased nutrient absorption[4,5].

Although it was believed that gut hormone secretion was the result of direct EEC sensing of nutrients in the lumen of the intestine, until recently little was known about the initial molecular recognition events involved in the enteroendocrine luminal sensing.

G protein-coupled receptors (GPCR) and intestinal nutrient sensing

G protein-coupled receptors (GPCR) represent the largest family of cell-surface mediators of signal transduction[6]. They are encoded by about 800 different genes in humans[7], enabling cells to respond to many diverse sensory inputs. Hence, GPCR are well-established targets for almost half of all therapeutic drugs, yet many are denominated as "orphan receptors" whose physiological agonists remain unknown. As such these receptors have attracted significant attention in terms of continued identification and characterisation, with recognition that they are potential targets for novel drug discovery. With more recent evidence that nutrient sensing in the gastrointestinal tract is accomplished by a number of GPCR[8], the role of these receptors as important nutritional targets is becoming increasingly evident.

Nutrient-sensing GPCR are categorised as either class A or class C. GPCR belonging to class C, such as the calcium sensing receptor (CaSR) and the taste 1 family receptors (T1R) are comprised of an N-terminal signal sequence, seven transmembrane domains coupled with a large extracellular domain (Venus flytrap module) and C-terminal cytoplasmic domain. Class A receptors such as fatty acid receptors also have seven transmembrane domains, but lack the Venus flytrap module[9]. In general, nutrient sensing GPCR are classified based on their α-subunits and the corresponding downstream signalling pathways they recruit. They are grouped into families $G_{\alpha s}$, $G_{\alpha i}$, $G_{\alpha q}$, $G_{\alpha 12/13}$, and gustducin. The physiological effects produced by these receptors in response to nutrients are mainly mediated via cyclic adenosine monophosphate (cAMP) and Ca^{2+} signalling cascades. Gαs stimulates adenylate cyclase (AC) leading to an increase in intracellular concentration of cAMP. $G_{\alpha i}$ inhibits AC resulting in decreased intracellular cAMP. $G_{\alpha q}$ stimulates phospholipase C (PLC) resulting in the generation of diacylglycerol (DAG) and inositol triphosphate (IP3), which respectively activate protein kinase C (PKC) triggering Ca^{2+} release from intracellular stores. $G_{\alpha 12/13}$ couples to the activation of the small G-protein Rho. Gustducin, a heterotrimeric G protein and mainly a member of $G_{\alpha i}$ family, can stimulate phosphodiesterase resulting in cAMP degradation, but in parallel the co-released $G_{\beta\gamma}$ subunits activate PLC-β2 leading to IP3 mediated Ca^{2+} release. The consequent elevation of cytoplasmic Ca^{2+} activates the Ca^{2+}sensitive transient receptor potential channel M5 (TRPM5) triggering membrane depolarization and opening of voltage-gated Ca^{2+} channels[9,10]. It has also been reported that gustducin activation stimulates adenylate cyclase, increasing cAMP directly or indirectly closing basolateral K^+ channels and triggering membrane depolarisation[11].

Several nutrient-sensing GPCR have been identified in the intestinal epithelium. They are expressed mainly on the apical membrane domain of enteroendocrine cells and are directly activated by a variety of nutrients. These include receptors for glucose, amino acids, peptides, protein hydrolysates, calcium and both long and short chain fatty acids (Fig.1)[12]. Nutrient sensing initiates a cascade of events involving hormonal and neural pathways. This culminates in functional responses that ultimately regulate vital physiological processes including food intake (appetite and satiety), nutrient digestion and absorption, intestinal barrier function, gut motility, and insulin secretion.

This review focuses on G protein-coupled receptors responsive to digestive products of macronutrients.

Carbohydrates

One of the primary functions of carbohydrates is to provide body energy. They comprise of sugars, digestible polysaccharides (such as starch) and non-digestible carbohydrates consisting of plant-based fibres and non-starch polysaccharides. In the small intestine, digestible polysaccharides are hydrolysed by pancreatic amylase and brush border membrane disaccharidases to constituent monosaccharides, glucose, galactose and fructose[13]. Non-digestible carbohydrates which escape digestion in the small intestine, reach the large intestine where they are fermented by gut microbiota, predominantly to short chain fatty acids.

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). A well- known example of gastrointestinal chemosensation (the incretin effect) is the observation that orally ingested glucose is a much more effective stimulator of insulin secretion from the pancreas than is intravenously injected glucose[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, PLCβ-2, TRPM5, 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 secretion of GLP-1[16,18]. 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-enteroendocrine cells 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, that 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, TRPM5 and GLP-1, are expressed in the mucosa of human proximal intestine. Young et al. (2009) also reported that 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 work 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[4]. 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 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 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 GLP-1).

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 Na^+/glucose cotransporter 1, SGLT1[27,28]. 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 has 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 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 upregulate SGLT1 expression and activity in response to luminal glucose or sweeteners[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 concentration[27], and proposed to be due to alterations in the mechanisms and signalling pathways involved in regulation of SGLT1 activity and expression.

As noted above, 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 T1R2-T1R3

Post weaning intestinal disorders are major health problems for the young. Weaning-associated diarrhoea, dehydration, and nutrient malabsorption results in high levels of mortality in farm animals worldwide. The findings 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[31,36,37]. Modulation of human intestinal T1R2-T1R3 activity may also have applications in humans 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 stimulating secretion of a range of gut hormones including CCK, GLP-1 and PYY[38]. The satiety effects associated with high-protein diets may also be mediated by sensing of the amino-acid constituents of proteins.

Intestinal sensing of protein hydrolysis products

Intestinal 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 ortholog GPCR6A, and the metabotropic glutamate receptors (mGluR).

CaSR is a homodimeric receptor that predominantly couples to Gαq, activating phosphatidylinositol (PI)-specific PLC and inducing mobilisation of intracellular Ca^{2+}[39]. However, it also couples to $G_{\alpha s}$, $G_{\alpha i}$ and $G_{\alpha 12/13}$[40]. CaSR is a multimodal sensor for several key nutrients, notably Ca^{2+} ions and L-amino acids, and is expressed abundantly throughout

the gastrointestinal tract[39,41]. Although it acts as a sensor for Ca^{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-, 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 STC-1 cells, it was shown that extracellular presence of L-phenylalanine (Phe) induced mobilisation of intracellular Ca^{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-Phe mediated Ca^{2+} responses and CCK release[44], indicating that CaSR plays a significant role in the chemosensing of amino acids in the GI tract.

GPRC6A is a $G_{q/11}$-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 GPRC6A is involved in L-ornithine (Orn)-induced GLP-1 release in the intestinal L-cell line GLUTag[47,48]. However, Oya *et al.* (2013) were unable to measure L-Orn-induced GLP-1 release from mixed primary cultures of mouse small intestine[48]. There are equally conflicting results using GPRC6A knockout mouse models. Alamshah *et al.* (2016) demonstrated that L-arginine (Arg) induced secretion of PYY from both wild type and GPRC6A KO mouse primary colonic L cells[49]. Jørgensen & Bräuner-Osborne (2020) addressing the *in vivo* relevance of these findings, administered L-Orn and L-Arg orally to the full locus and exon VI GPRC6A 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 GPRC6A, *in 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 GPRC6A in intestinal chemosensing.

Taste 1 receptor 1 and receptor 3 (T1R1-T1R3).

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 (Glu)[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 (Trp)[52]. 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 Glu analogue l-AP4)[22,51,53]. The T1R1-T1R3 heterodimer, like the sweet receptor T1R2-T1R3, is expressed in EEC[15] and is coupled to gustducin for the transmission of intracellular signals[54]. 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[55]. Using siRNA to inhibit expression of T1R1 mRNA and protein in STC-1 cells, it was demonstrated that 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 significant decline in Phe-, leucine- and Glu-induced CCK release. Conversely, Trp- induced CCK secretion was unaffected by inhibition of T1R1 expression, in agreement with Trp not being an agonist for T1R1-T1R3[55].

Thus, both CaSR and T1R1-T1R3 have been recognized as intestinal L-amino acid sensors mediating CCK secretion in response to aromatic amino acids such as L-Phe[44,55]. 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[55].

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[56]. Further work is required to elucidate the peptone-sensing role of this GPCR, if any, in the intestine.

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 (omega-6) and α-linoleic (omega-3) acid that

cannot be *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 secretion of a number of gut hormones, including CCK, GLP-1 and GIP[57]. It is reported that long chain fatty acids (LCFA) inhibit gastric emptying and induce satiety[58], with short chain fatty acids (SCFA) eliciting GLP-1 and PYY secretion[59].

Intestinal fatty acid sensing

There are four principal GPCR, FFA1-FFA4, that have been officially classified as members of a free fatty acid 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 Gαq-coupled[60]. The supporting evidence that long chain fatty acid receptors contribute directly to intestinal fatty acid chemosensing is from the findings that their expression in GI tract is largely limited to the enteroendocrine cell population. The pattern of expression of FFA4 in enteroendocrine cells appears to be similar to that of FFA1. This has highlighted the need for highly selective ligands to probe their functions. Based on these observations, a number of preclinical and clinical developmental programmes have explored the therapeutic potential of agonists of FFA1. Indeed, some synthetic agonists of FFA1 have shown the capacity to improve glycaemic control in diabetes. However, questions remain in terms of sustainability of effects during long term treatment[60]. There are conflicting experimental evidence relating to the roles of FFA1 and FFA4[61-63] and is not clear which one plays the more important role in enteroendocrine fatty acid sensing. 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[60].

The short chain fatty acid (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 (C2), propionate (C3) and butyrate (C4). FFA2 responds to C2-C3 fatty acids and couples to Gαi/o as well as Gαq,

whereas FFA3 preferentially binds C3-C5 and couples only to Gαi/o. These SCFA are generated predominantly in the distal gut by microbial fermentation of non-digestible carbohydrates, such as fibre and non-starch polysaccharides. It has been reported that non-digestible and fermentable dietary fibre and starch, as well as SCFA themselves, enhance GLP-1 secretion[64]. Moreover, the SCFA-induced release of GLP-1 from EEC appears to be mediated by FFA2[65].

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[66]. 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[67]. Thus, the physiological role of SCFA receptors, and their relative importance, compared with other possible targets of prebiotic supplementation remains to be established.

Other free fatty acid 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 $G_{\alpha s}$ and is responsive to monoacylglycerols, products of triglycerides hydrolysis. It is proposed that small-molecule ligands of GPR119 increase GLP-1, GIP and insulin release[68], however studies have shown these ligands have limited glucose lowering and incretin activity in subjects with type 2 diabetes[69].

Concluding remarks

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 gastrointestinal 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

The authors declare that there is no conflict of interest.

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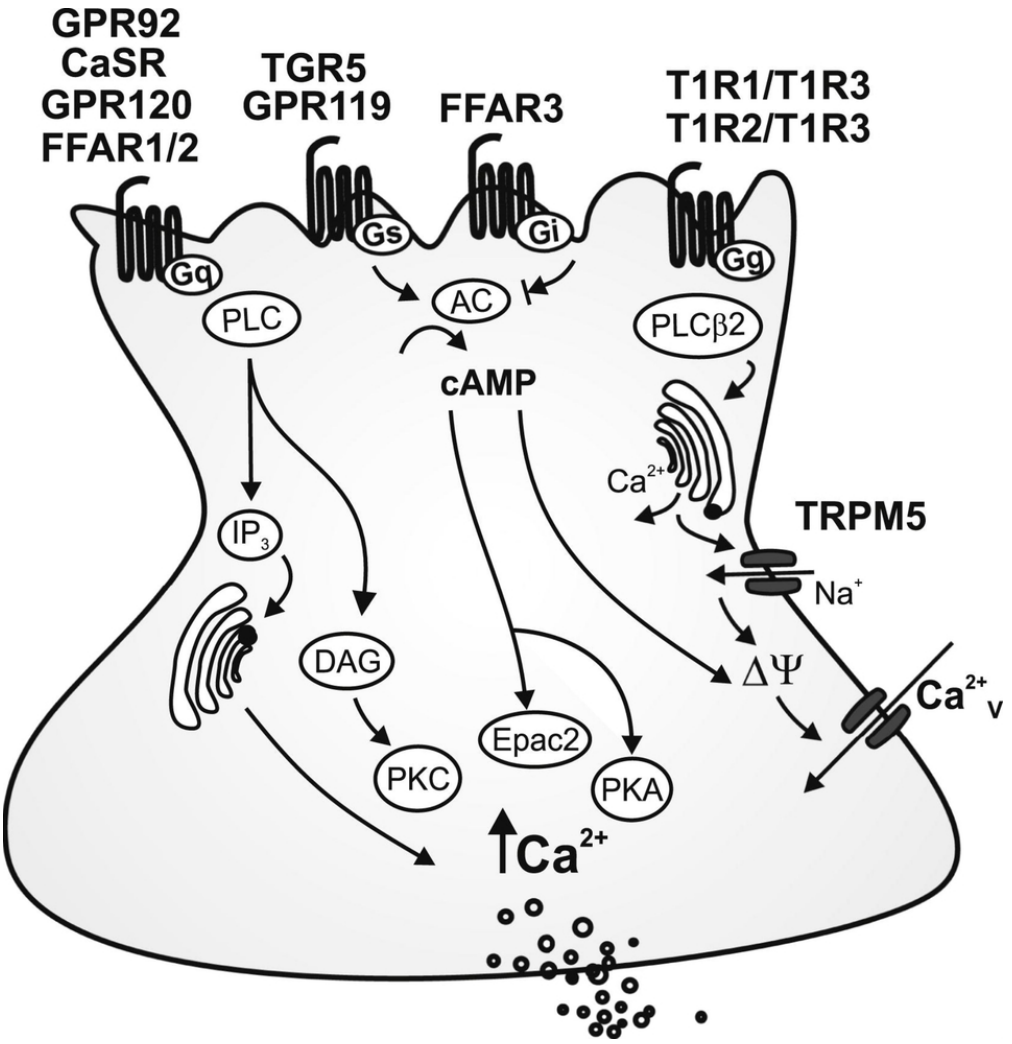

A schematic diagram of an enteroendocrine cell with luminal-facing nutrient sensing G protein-coupled receptors and downstream signalling pathways. Taken from Reimann et al. (2012)(12) with permission from Cell Press.

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