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S. P. Shirazi-Beechey, A. W. Moran, D. J. Batchelor, K. Daly and M. Al-Rammahi

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Symposium on ‘Nutrition: getting the balance right in 2010’

Session 3: Influences of food constituents on gut health Glucose sensing and signalling; regulation of intestinal glucose transport

S. P. Shirazi-Beechey*, A. W. Moran, D. J. Batchelor, K. Daly and M. Al-Rammahi

Epithelial Function and Development Group, Department of Cellular and Molecular Physiology, Institute of Translational Medicine, Faculty of Health and Life Sciences, University of Liverpool, Liverpool L69 7ZJ, UK

Epithelial cells lining the inner surface of the intestinal epithelium are in direct contact with a luminal environment that varies dramatically with diet. It has long been suggested that the intestinal epithelium can sense the nutrient composition of luminal contents. It is only recently that the nature of intestinal nutrient-sensing molecules and underlying mechanisms have been elucidated. There are a number of nutrient sensors expressed on the luminal membrane of endocrine cells that are activated by various dietary nutrients. We showed that the intestinal glucose sensor, T1R2+T1R3 and the G-protein, gustducin are expressed in endocrine cells. Eliminating sweet transduction in mice *in vivo* by deletion of either gustducin or T1R3 prevented dietary monosaccharide- and artificial sweetener-induced up-regulation of the Na⁺/glucose cotransporter, SGLT1 observed in wild-type mice. Transgenic mice, lacking gustducin or T1R3 had deficiencies in secretion of glucagon-like peptide 1 (GLP-1) and, glucose-dependent insulinotropic peptide (GIP). Furthermore, they had an abnormal insulin profile and prolonged elevation of postprandial blood glucose in response to orally ingested carbohydrates. GIP and GLP-1 increase insulin secretion, while glucagon-like peptide 2 (GLP-2) modulates intestinal growth, blood flow and expression of SGLT1. The receptor for GLP-2 resides in enteric neurons and not in any surface epithelial cells, suggesting the involvement of the enteric nervous system in SGLT1 up-regulation. The accessibility of the glucose sensor and the important role that it plays in regulation of intestinal glucose absorption and glucose homeostasis makes it an attractive nutritional and therapeutic target for manipulation.

Intestine: Glucose sensor: Nutrient: Neuroendocrine: SGLT1

The intestinal epithelium is lined with a single layer of epithelial cells that undergoes rapid and continuous renewal. The stem cell located near the base of the crypt of Lieberkühn gives rise to absorptive enterocytes, and three types of secretory cells; mucus producing goblet, Paneth and enteroendocrine. Paneth cells, which secrete antimicrobial peptides, digestive enzymes and growth factors, complete their differentiation at the crypt base. The other three epithelial lineages differentiate during a highly organised upward migration from the crypt to the villus tip where they are extruded into the intestinal lumen^(1,2). This process takes about 2–3 d in most species^(3–5).

Enterocytes constitute the majority (90%) of cells lining the villus (Fig. 1). They are involved in vectorial transport

of nutrients from the lumen of the intestine to the systemic system. These polarised cells possess two distinct membrane domains, the apical (brush border) and basolateral. These membranes differ in structure, function and surface charges⁽⁶⁾; properties that have facilitated their isolation in pure form as brush-border or basolateral membrane vesicles. Brush-border membrane vesicles have been used frequently for measurements of digestive enzyme activities and nutrient transport functions expressed on the brush-border membrane⁽⁷⁾.

Enteroendocrine cells, dispersed among the cells lining the intestinal epithelium, represent about 1% of the entire gut epithelial population (Fig. 1), but collectively they are the largest endocrine organ of the body⁽⁸⁾. They are flask

Abbreviations: ENS, enteric nervous system; GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2; GIP, glucose-dependent insulinotropic peptide.

*Corresponding author: Professor Soraya P. Shirazi-Beechey, fax +44 151 794 4244, email spsb@liverpool.ac.uk

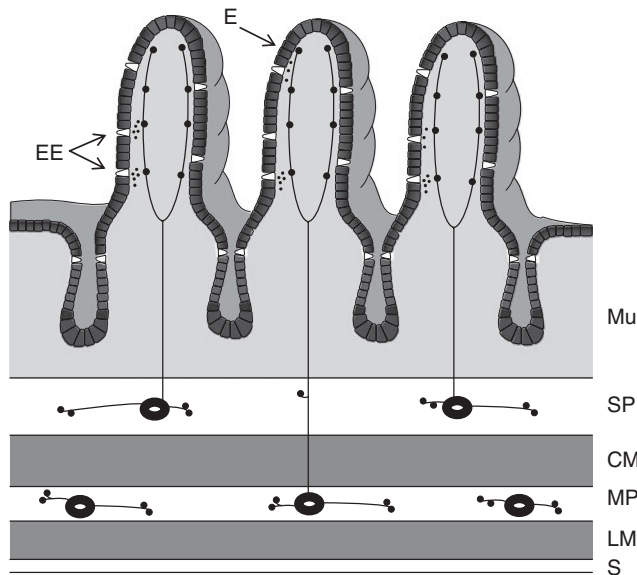


Fig. 1. Schematic diagram showing the organisation of small-intestinal tissue. The surface of the small intestine consists of numerous villi which are lined with a single layer of epithelial cells, 90% of which are absorptive enterocytes (E). Enterocytes are involved in vectorial transport of nutrients from the lumen of the intestine to the systemic system. Enteroendocrine (EE) cells are dispersed among enterocytes and act as 'sensor' cells of the gut. They respond to changes in gut content by releasing peptides. Neurons in the enteric nervous system are arranged in two major ganglionated plexuses: The myenteric plexus (MP) lies between the longitudinal muscle (LM) and circular muscle (CM) and the submucosal plexus (SP) is associated with the mucosal (Mu) epithelium. The nerve endings of afferent nerves, that transmit changes in nutrient content of the gut lumen, do not penetrate the epithelial cell layer to reach the intestinal lumen. The information about the chemical nature of the luminal content is signalled to nerve terminals by EE cells releasing peptides in response to luminal nutrients. Mu, mucosa; S, serosa.

shaped with the majority having long, slender apical processes directly in contact with the gut lumen, where they can 'sample' the luminal contents. These cells respond to changes in gut contents by releasing various peptides. At least twenty different endocrine cell subpopulations have been defined based on their principal endocrine products⁽⁹⁾. For example, in response to dietary carbohydrates, enteroendocrine cells secrete a number of gut peptides such as glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), glucose-dependent insulintrophic peptide (GIP) and serotonin. GLP-1 and GLP-2 are released by endocrine L-cells, while K-cells secrete GIP^(10,11). L-cells are found scattered throughout the small and large intestine, with the highest density in the distal ileum and colon⁽¹²⁾. L-cells, however, have also been identified at low density in the duodenum⁽¹³⁾ and in higher numbers in the jejunum⁽¹²⁾. K-cells are predominantly located in the duodenum. Interestingly, a proportion of cells in the proximal small intestine express both GLP-1 and GIP^(13,14). Enterochromaffin cells, a subset of enteroendocrine cells, secrete serotonin in response to dietary carbohydrates. The number of enterochromaffin cells increases aborally⁽¹⁵⁾. These gut hormones play essential roles in vital processes including

control of gastric emptying, gut motility, stimulation of insulin secretion (incretin effect), nutrient absorption and appetite regulation.

The enteric nervous system (ENS) is necessary for the digestive and interdigestive states of activity of vasculature, the smooth muscle and the epithelium⁽¹⁶⁾. The ENS is capable of functioning independently of the central nervous system and contains an estimated 10^8 neurons in two major ganglionated plexuses that extend the entire length of the bowel in two major layers: the myenteric plexus lies between the longitudinal and circular muscle and the submucosal plexus is associated with the mucosal epithelium (see Fig. 1). Neurons of the myenteric plexus send most of their axonal projections to the muscle layers of the intestine. Submucosal plexus neurons, however, send the majority of their projections to the subepithelial regions⁽¹⁷⁾. More than sixteen phenotypically distinct neuronal populations have been identified and classified, by their morphology, transmitter content and electrophysiological properties, into sensory neurons, ascending and descending interneurons and excitatory and inhibitory motor neurons⁽¹⁸⁾. The capacity of the ENS to regulate gut behaviour autonomously depends on the presence of elements for coding sensory stimuli, integration of information and motor innervation to the muscle and mucosa. Intrinsic primary afferent neurons of the ENS are transducers of physiological stimuli, including movements of the villi, contraction of intestinal muscle and changes in the composition of the contents of the gut lumen⁽¹⁸⁾. However, the nerve endings of both intrinsic and extrinsic afferent nerves, responsible for transmitting changes in nutrient content of the gut lumen, do not penetrate the epithelial cell layer to reach the intestinal lumen (Fig. 1). Thus, it is likely that information about the chemical nature of the luminal contents is signalled to these primary afferent nerve terminals by cells in the epithelial layer. The most probable candidates are the endocrine cells as they are known to release gut hormones in response to luminal nutrients. Enteroendocrine cells are now regarded as being pivotal to the chemosensing pathways of the intestinal tract (see later). Recent identification of nutrient sensors, a family of G-protein-coupled receptors expressed on the luminal membrane of enteroendocrine cells, has revealed mechanisms by which luminal nutrients are sensed by endocrine cells, eliciting secretion of gut hormones.

This review focuses on intestinal glucose sensing and its role in regulation of intestinal glucose absorption. Experimental evidence suggesting the involvement of a neuroendocrine mechanism regulating intestinal glucose transport and the capacity of the gut to absorb glucose will be highlighted.

Intestinal glucose transport

Glucose and galactose are transported across the apical membrane of enterocytes by Na^+ /glucose cotransporter 1, SGLT1 (Fig. 2). Absorption of glucose (and galactose) is coupled to Na^+ and its associated electrochemical gradient; the latter provided by the activity of basally located Na^+/K^+ -ATPase^(6,19). Fructose is transported by the

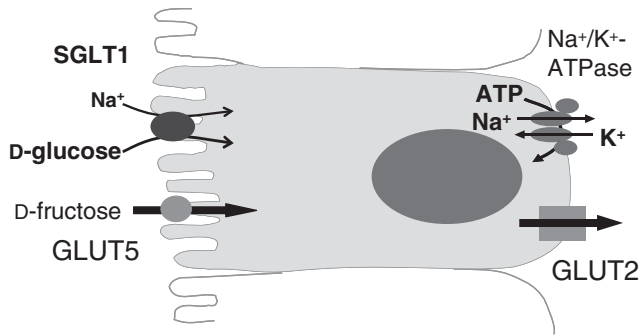


Fig. 2. The image shows a schematic diagram of an enterocyte with Na⁺/glucose cotransporter (SGLT1), and fructose transporter (GLUT5) on the luminal membrane and the monosaccharide transporter (GLUT2) on the basal membrane.

Na⁺-independent fructose transporter, GLUT5, transporting fructose from the lumen of intestine into enterocytes down its concentration gradient. These monosaccharides, when accumulated in the enterocytes, exit the cell across the basolateral membrane into the systemic system by another Na⁺-independent monosaccharide transporter, GLUT2; a bidirectional transporter that can move glucose out or into the cell depending on its concentration gradient⁽⁶⁾. SGLT1 has been shown to be expressed on the brush-border membrane of villus enterocytes in most mammalian species studied^(20–25). In general, expression levels are higher in jejunum > duodenum > ileum. SGLT1 is not expressed in any epithelial cells of mammalian large intestine^(26,27).

It has been suggested by some, that in rat intestine, *in vivo* under anaesthesia, when luminal glucose or fructose concentration is high, GLUT2 is rapidly recruited to the brush-border membrane of absorptive enterocytes, where it can transport both glucose and fructose^(28–30). It has been argued that GLUT2 has a higher capacity but a lower affinity than SGLT1 for glucose and it is not saturated even at glucose concentrations over 100 mM⁽²⁸⁾. It is important to note that kinetic parameters are properties of a protein and are not indicators of its capacity. The capacity of a system depends on the number of transporters in the membrane and the rate by which the substrate is translocated across the membrane. Furthermore, the evidence from knockout animal models and from human subjects with mutated transporters argues against the presence of GLUT2 on the brush-border membrane. GLUT2 knockout mice, and individuals with inactivating mutations in GLUT2 (Fanconi–Bickel syndrome) do not have any demonstrable defect in intestinal glucose absorption^(31,32). The presence of apical GLUT2 should enable fructose absorption when GLUT5 activity is limiting; however, GLUT5 knockout mice cannot absorb fructose, even when their intestine is infused with high concentrations of glucose or fructose⁽³³⁾. In addition, immunohistochemistry using two different antibodies raised against peptides corresponding to the C-terminal region, or to residues 40–55 of the GLUT2 amino acid sequence has demonstrated that the GLUT2 protein is exclusively located on the basolateral membrane of enterocytes^(23–25). Therefore, the body of evidence suggests that SGLT1 is the major route for the

transport of dietary sugars from the lumen of the intestine into enterocytes. Regulation of this protein is essential for the provision of glucose to the body. This has important nutritional and clinical implications.

Regulation of intestinal glucose transport

Work in various laboratories has shown that, in the majority of species (see exceptions later), monosaccharides in the lumen of the intestine directly regulate SGLT1 expression^(5,34–36). Intestinal infusions with glucose or galactose (metabolisable substrates of SGLT1), α -methylglucose and 3-*O*-methyl glucose (non-metabolisable substrates of SGLT1) and fructose (not a substrate of SGLT1), resulted in up-regulation of SGLT1 expression, indicating that a wide range of monosaccharides are effective in enhancing the expression of SGLT1 and that metabolism of the monosaccharide is not required^(34,35,37). The increase in SGLT1 was not accompanied by any changes in surface area for absorption⁽³⁸⁾. Furthermore, the introduction of membrane impermeable glucose analogues to the lumen of the intestine also stimulated SGLT1 expression⁽³⁹⁾. The latter finding led to the conclusion that there is a glucose sensor on the gut luminal membrane responsible for detecting luminal sugars leading to modulations in SGLT1 expression. The membrane impermeable analogues, however, had no inhibitory effect on Na⁺-dependent glucose transport function, ruling out SGLT1 as the glucose sensor. Further work, using *in vitro* models, suggested that sugar-mediated up-regulation of SGLT1 is likely to involve a G-protein-coupled second-messenger pathway⁽³⁹⁾.

Sweet taste receptor of lingual epithelium

The sweet taste receptor expressed in taste cells of lingual epithelium is a heterodimer of T1R2+T1R3 subunits that couple through the gustatory G-protein gustducin⁽⁴⁰⁾ to specific second-messenger cascades. Based on heterologous expression of taste receptors and behavioural assays of transgenic (T1R2, T1R3, gustducin knockout) mice, the combination of T1R2+T1R3 was shown to function as a broad-specificity sweet sensor for natural sugars, sweet proteins and artificial sweeteners^(41,42). The heterodimer of T1R2 and T1R3 can respond to almost all sweet molecules with diverse chemical structures⁽⁴³⁾. There are also structural and sequential variations of the sweet taste receptor in various species⁽⁴⁴⁾. Recent investigations demonstrate different functional roles of the subunits as well as the presence of discrete sites responsible for binding ligands of different chemical structures⁽⁴⁵⁾.

In lingual epithelium, the key elements of taste transduction pathways are α -, β - and γ -subunits of gustducin, phospholipase C β 2 and transient receptor potential melastatin 5, a Ca²⁺-activated cation channel^(46–48).

Intestinal glucose sensor

With respect to the intestinal epithelium, α -gustducin was shown to be present in brush cells of rat proximal intestine⁽⁴⁹⁾, in mouse intestinal endocrine cells and in a murine

endocrine cell line⁽⁵⁰⁾, suggesting that taste-sensing mechanisms may exist in the gastrointestinal tract.

Our laboratory was first to show that T1R2 and T1R3 are expressed in the rodent gut and the enteroendocrine STC-1 cell line⁽⁵¹⁾ and proposed that they function as the luminal sugar sensor to control SGLT1 expression in response to dietary sugars. Subsequently, we demonstrated that T1R2, T1R3 and the α -subunit of gustducin are co-expressed in K- and L- endocrine cells in a wide range of species including human, mouse⁽²⁰⁾, dog⁽²⁵⁾ and pig⁽⁴⁴⁾. In pig intestine, these glucose sensing elements are also expressed together in enterochromaffin cells containing serotonin. However, enterochromaffin cells expressing T1R2, T1R3 and gustducin were few and far between compared to L- or K-cells expressing these sensing elements (10% *v.* 50%, respectively)⁽⁴⁴⁾.

Using the GLUTag cell line, derived from endocrine colonic tumours, and intestinal primary cells, Parker *et al.* have proposed that secretion of GLP-1 by L-cells and GIP by K-cells is through uptake of the monosaccharide by SGLT1; secretion of these gut hormones was inhibited by the drug, phlorizin. They have suggested that SGLT1 is the likely mediator of the direct responsiveness of K- and L-cells to luminal sugars⁽⁵²⁾. It must be noted that phlorizin is a non-selective inhibitor of SGLT1 with a poor bioavailability as most of the drug is metabolised to phloretin, the aglycone of phlorizin⁽⁵³⁾. In addition to inhibiting SGLT1 function, it affects many other processes including inhibition of the epithelial Cl/HCO₃ exchanger⁽⁵⁴⁾ and signal transduction pathways⁽⁵⁵⁾. Furthermore, SGLT1 is not expressed in any epithelial cells (this includes absorptive epithelial and enteroendocrine cells) of the colon^(26,27) where there are ample GLP-1 secreting L-cells. These findings shed doubt on the role of SGLT1 as a glucose sensor initiating gut hormone release.

T1R3 and gustducin in the gut sense dietary sugars to regulate expression of SGLT1

Convincing evidence for the involvement of the sweet receptor and gustducin in intestinal sweet transduction was provided by studies using mice in which the genes for either α -gustducin or the sweet receptor subunit, T1R3, were deleted (knockout mice). Eliminating sweet taste transduction in mice *in vivo* by deletion of either α -gustducin or T1R3 prevented dietary monosaccharide-induced up-regulation of SGLT1 expression that was observed with wild-type mice^(20,56). In wild-type mice maintained on a high-carbohydrate diet (70% sucrose), there was a 2-fold increase in the steady-state level of SGLT1 mRNA and protein abundance compared with mice fed an iso-energetic low-carbohydrate (1.9% sucrose) diet. This increase correlated quantitatively with an increase in the initial rate of Na⁺-dependent glucose transport into isolated brush-border membrane vesicles. T1R3- and gustducin-knockout mice, however, showed no change in SGLT1 mRNA, protein and function on either diet. Therefore, knocking out either α -gustducin or T1R3 abolishes the ability of mouse intestine to increase SGLT1 expression in response to increased dietary carbohydrate⁽²⁰⁾.

The expression of SGLT1 in both types of knockout mice was identical to that of wild-type animals on the low-carbohydrate diet⁽²⁰⁾. This suggests that there is a constitutive level of SGLT1 expression, independent of luminal sugar sensing by T1R3 and/or α -gustducin that maintains basal SGLT1 expression levels, and an inducible pathway, dependent on T1R3 and gustducin that regulates SGLT1 expression in response to luminal sugars⁽²⁰⁾. In support of this, we have recently shown that when piglets were maintained on iso-energetic diets containing increasing concentrations of carbohydrate (7, 36, 53 or 60%), SGLT1 expression remained constant on the 7 and 36% carbohydrate diets, but there was an increase in SGLT1 expression when the carbohydrate content of the diet exceeded 50%⁽²⁴⁾. Collectively, the data indicate that the intestine has the capacity to absorb glucose via basal levels of SGLT1, but that this capacity becomes limiting when dietary carbohydrate exceeds a certain level.

SGLT1 expression is not responsive to dietary carbohydrates in naturally occurring T1R2 mutants

Characterisation of vertebrate genome sequences has shown that the T1R2 gene is absent in the chicken and is an unexpressed pseudogene in cats^(57,58). Among birds, a characteristic response to sweet stimuli is absent in the chicken⁽⁵⁹⁾, and the domestic cat, as well as other members of the *Felidae* family of obligate carnivores, tiger and cheetah, show no preference for and cannot taste sugars⁽⁵⁸⁾. In consideration of these findings, with respect to intestinal sugar sensing and SGLT1 up-regulation, it has been shown that cats cannot upregulate SGLT1 expression in response to increased dietary carbohydrate levels⁽⁶⁰⁾. Furthermore, it has been reported that expression of SGLT1 in chicken intestine was unresponsive to increased luminal glucose⁽⁶¹⁾. As both subunits of the heterodimeric T1R2+T1R3 are required for sweet-responsiveness, the loss of T1R2 in cats and chicken provides the genetic explanation for the lack of response of SGLT1 to changes in dietary carbohydrate in these species; these animals are incapable of detecting luminal sugars. Therefore, in these 'naturally occurring knockout' models there is a good correlation between the absence of T1R2 expression and the inability to increase SGLT1 in response to increased dietary sugars.

Effect of artificial sweeteners on SGLT1 expression

Artificial sweeteners sucralose, saccharin, acesulfame K and aspartame taste sweet to humans. However, aspartame does not taste sweet to mice and does not stimulate expressed mouse T1R2+T1R3⁽⁴²⁾. It has been shown that in wild-type mice maintained on a low-carbohydrate diet consuming sucralose-sweetened water, there is a 2-fold increase in SGLT1 expression compared with the wild-type controls; the latter being maintained on the same low carbohydrate but given plain water. In contrast, in response to supplementation with sucralose, neither the T1R3 nor the gustducin knockout mice show an increase in SGLT1 expression, suggesting that the sweet receptor is involved in sensing the presence of not only monosaccharides,

but also artificial sweeteners in the intestinal lumen⁽²⁰⁾. Interestingly, in wild-type mice, consuming the low-carbohydrate diet with artificial sweetener-containing water, SGLT1 expression was increased 1.8- and 1.9-fold in response to saccharin and acesulfame K, but there was no increase in response to aspartame⁽²⁰⁾. The responsiveness of the intestinal sweet sensor to various artificial sweeteners appears to be similar to that of the sweet taste receptor of the lingual epithelium. Such a similarity has also been observed in responsiveness of swine intestinal sweet receptor⁽⁴⁴⁾.

Communication between the chemosensory endocrine cells and absorptive enterocytes

The intestinal glucose sensor T1R2+T1R3, and the transducer G-protein, gustducin are expressed and associated with the luminal membrane of enteroendocrine cells and are required for enhanced expression of SGLT1 by enterocytes *in vivo* in response to luminal sugars and sweeteners⁽²⁰⁾. The question that arises is how does activation of the sensor in the enteroendocrine cell cause increased expression of SGLT1 in neighbouring enterocytes? It is known that endocrine cells can exert biological effects by releasing hormones that can either influence nearby cells directly, enter the bloodstream to act distantly as hormones, or activate nearby vagal and spinal afferent fibres from the neurons within the nodose and dorsal root ganglia, respectively, as well as the enteric neurons⁽⁶²⁾.

There is an increasing body of evidence to support that systemic application of the gut hormone, GLP-2, leads to up-regulation of SGLT1 expression⁽⁶³⁻⁶⁶⁾. While there is one study suggesting that GIP is involved in enhancing SGLT1 expression⁽⁶⁷⁾, no data as yet are available on the potential role of GLP-1 in this process. For these gut hormones to exert their effects they must bind to their specific receptors. The exact cellular location of GLP-2 receptor has been the subject of controversy. However, there is a greater consensus, based on solid experimental evidence, that GLP-2 receptor is not expressed in any surface epithelial cells, but is present in the enteric neurons^(68,69). Work in our laboratory, using immunohistochemistry, has identified that GLP-2 and GIP receptors, but not GLP-1 receptor, are expressed in enteric neurons of mouse and pig intestine (M Al-Rammahi and SP Shirazi-Beechey, unpublished results). Our finding on the location of GLP-2 receptor is consistent with that reported in guinea pig ileum and mouse jejunum^(68,69). The role of GIP in eliciting SGLT1 up-regulation is however doubtful. Wild-type and GIP receptor knockout mice, when maintained on a high-carbohydrate diet, both showed 2-fold increase in SGLT1 expression compared to their counterparts maintained on a low-carbohydrate diet (M Hosokawa, N Harada and SP Shirazi-Beechey, unpublished results).

Bjerknes and Cheng have shown that enteric neurons respond to GLP-2 administration and induce a response in progenitors of absorptive enterocytes⁽⁶⁹⁾; this response can be blocked by local inhibition of neuronal transmission. Preliminary work in our laboratory has indicated that stimulation of enteric neurons, using electric field stimulation, results in SGLT1 up-regulation, proposing the

involvement of the ENS in SGLT1 regulation. In support of this, Debnam has shown that raised luminal glucose concentrations in the ileum result in up-regulation of SGLT1 in more proximal (jejunum) small intestine⁽⁷⁰⁾. Furthermore, Sharp *et al.* have reported that up-regulation of SGLT1 in response to high luminal glucose was only achieved in intact mucosa, and not in isolated enterocytes⁽⁷¹⁾; both studies proposing the involvement of neural mechanisms underlying SGLT1 up-regulation.

Intracellular pathways underlying SGLT1 regulation in absorptive enterocytes

There is strong evidence that increases in intracellular 3', 5'-cyclic AMP (cAMP) in enterocytes leads to increased SGLT1 expression⁽⁷²⁻⁷⁵⁾. SGLT1 expression was impaired in a protein kinase A-(cAMP-dependent protein kinase) deficient mutant⁽⁷⁶⁾ and forskolin (which stimulates adenylate cyclase) enhanced Na⁺-dependent glucose transport in mouse intestine mounted in an Ussing chamber⁽⁷⁷⁾. In support of these observations, we have shown that exposure of enterocytic type cells to cAMP-elevating agents, such as forskolin, or a membrane permeable analogue of cAMP, 8-bromo-cAMP, results in about a 2-fold increase in SGLT1 expression (D Batchelor and SP Shirazi-Beechey, unpublished results). Lofin and Lever have also shown that a number of cAMP-elevating agents increase SGLT1 expression at levels of mRNA, protein and function, and have demonstrated that post-transcriptional regulation of mRNA stability plays a major role in SGLT1 up-regulation⁽⁷⁸⁾. A uridine-rich regulatory sequence element in the 3'-untranslated region of SGLT1 mRNA has been identified^(79,80), which is critical for cAMP-dependent stabilisation of the mRNA⁽⁷⁹⁾.

Mechanisms governing sugar-stimulated SGLT1 up-regulation

The accumulated data suggest that the sweet receptor, T1R2+T1R3, expressed on the luminal membrane of villus endocrine cells, senses luminal glucose concentration. Luminal glucose, above a threshold, activates a signalling pathway in endocrine cells involving T1R2+T1R3, gustducin and other signalling elements resulting in the secretion of GLP-1, GLP-2 and GIP^(20,56) (Fig. 3). We propose that GLP-2 binding to its receptor on enteric neurons elicits an action potential⁽⁶⁹⁾. This stimulus is transmitted to subepithelial regions, by the axonal projections that reach the basal membrane domain of absorptive enterocytes, evoking the release of a neuropeptide. Subsequent binding of this neuropeptide to its receptor on the basolateral membrane of enterocytes enhances intracellular cAMP levels, thereby increasing the stability of SGLT1 mRNA leading to enhanced levels of functional SGLT1 protein. The nature of the neuronal signal and the neuropeptide is as yet unknown. However, the knowledge that increases in intracellular cAMP in enterocytes cause increased SGLT1 expression, proposes that the receptor for the final effector in this pathway needs to be a stimulatory G-protein.

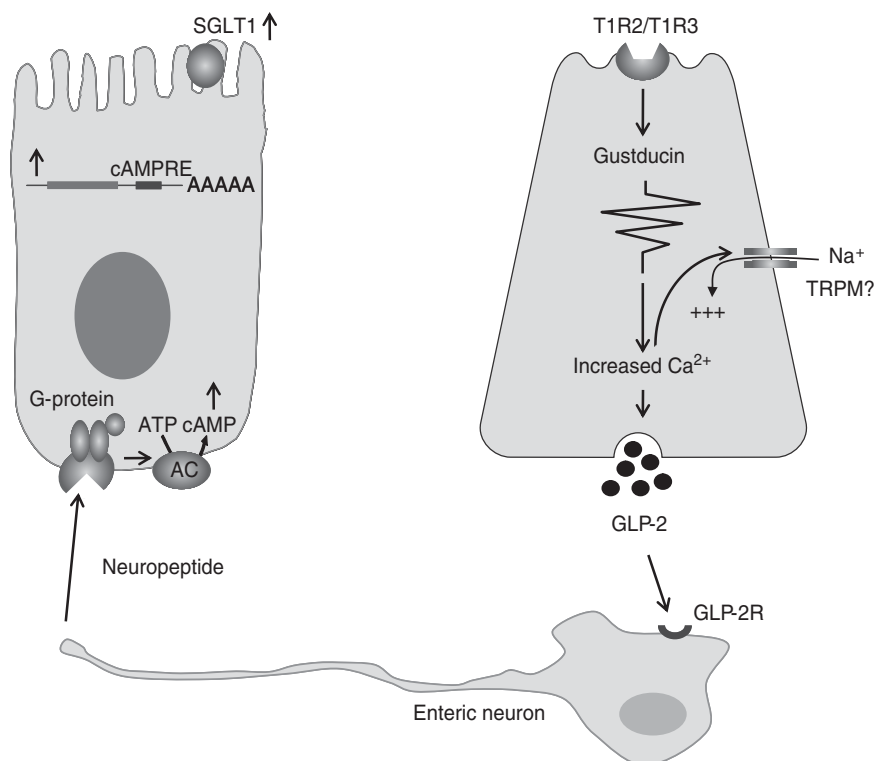


Fig. 3. Proposed pathways involved in regulation of the intestinal glucose transporter, Na^+ / glucose cotransporter, SGLT1, by dietary sugars. The glucose sensor, T1R2+T1R3, expressed on the luminal membrane of enteroendocrine cells, senses luminal glucose. Luminal glucose, above a threshold level, activates in endocrine cells a signalling pathway involving T1R2+T1R3, gustducin and other signalling elements, resulting in secretion of GLP-2. GLP-2 binds to its receptor (GLP-2R) on enteric neurons evoking an action potential, which is transmitted by axonal projections to the vicinity of basolateral membranes of enterocytes. Release of a neuropeptide that binds to its receptor on the basolateral domain of enterocytes evokes an elevation in levels of intracellular cAMP. This ultimately leads to an increase in the half-life of SGLT1 mRNA. AC, adenylyl cyclase; cAMPRE, cyclic AMP response element; TRPM, transient receptor potential melastatin (although in the lingual epithelium a transient Ca^{2+} activated cation channel member 5 (TRMP5) is a key element of the taste transduction pathway in the intestinal cells the nature of the isoform of this channel is not yet known).

Glucose is an important source of metabolic energy for the majority of mammalian cells. It is a precursor of carbohydrate moieties, as well as a component of macromolecules such as glycoproteins, proteoglycans and glycolipids. Therefore, glucose plays a central role in cellular homeostasis and metabolism. SGLT1 is the major route for the transport of dietary glucose (and galactose) from the lumen of the intestine into enterocytes. Regulation of this protein is essential for the provision of glucose to the body and avoidance of malabsorption.

The identification of molecular and cellular processes controlling SGLT1 expression will assist the recognition of nutritional and therapeutic targets for modulating the capacity of the intestine to absorb dietary glucose. This has important nutritional and clinical implications.

Summary and conclusions

Dietary sugars and artificial sweeteners enhance the expression of the intestinal glucose transporter SGLT1

and the capacity of the gut to absorb glucose. The underlying molecular mechanism is that the intestinal glucose sensor, T1R2+T1R3, expressed on the luminal membrane of enteroendocrine cells, senses the luminal monosaccharide concentration. Luminal monosaccharide, when above a threshold, activates, in endocrine cells, a signalling pathway involving T1R2+T1R3, gustducin and other signalling elements. This results in the secretion of a gut hormone, likely to be GLP-2. We propose that this hormone binds to its receptor on enteric neurons and through a neuroendocrine mechanism enhances SGLT1 expression in absorptive enterocytes. The accessibility of the glucose sensor and the important role that it plays in regulation of intestinal glucose absorption and glucose homeostasis makes it an attractive nutritional and therapeutic target for manipulation. Furthermore, the identification of mechanisms involved in regulation of intestinal glucose transport may provide a model for the regulation of other intestinal nutrient transporters.

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