Intestinal glucose sensing and regulation of intestinal glucose absorption


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Abstract

SGLT1 (Na+/-glucose co-transporter 1) transports the dietary sugars, α-glucose and α-galactose, from the lumen of the intestine into enterocytes. SGLT1 regulation has important consequences for the provision of glucose to the respiring tissues and is therefore essential for maintaining glucose homeostasis. SGLT1 expression is directly regulated in response to changes in the sugar content of the diet. To monitor these variations, there is a requirement for a glucose-sensing system located on the luminal membrane of gut cells. This short review focuses on recent findings on intestinal sugar sensing and the downstream mechanisms responsible for enhancement in SGLT1 expression.

Glucose in the lumen of the intestine evokes various changes in gastrointestinal function including gastric emptying, gut motility, secretion and absorption. The ability of the intestine to modulate its glucose-absorptive capacity is achieved through changes in expression of the intestinal SGLT1 (sodium/glucose co-transporter 1) [1]. It is now evident that in many species (see exceptions below), monosaccharides in the lumen of the intestine directly regulate SGLT1 expression [2–6]. The up-regulation of SGLT1 by luminal sugars is independent of glucose metabolism and is not accompanied by any changes in surface area for absorption [2,4,6,7]. Furthermore, the introduction of membrane-impermeable glucose analogues to the lumen of the intestine stimulates SGLT1 expression [6]. This implies that a glucose sensor on the luminal membrane is responsible for relaying information on the fluctuations in luminal sugar content, which leads to changes in SGLT1 expression. This sensing of glucose cannot be attributed to SGLT1 itself since the analogues did not inhibit Na+-dependent glucose transport activity. Further work, using intestinal cell lines transfected with SGLT1 promoter constructs containing a glucose-response element, has suggested that the sugar-mediated up-regulation of SGLT1 is likely to involve a G-protein-coupled second messenger pathway [6]. With this in mind, much of the recent emphasis has therefore been placed on identifying the intestinal glucose sensor and determining the downstream cellular events that its activation elicits.

Until recently, the only known mechanism for sensing glucose in the gastrointestinal tract was by sweet taste receptors located in taste cells of lingual epithelium [8,9]. Sugars and other sweet compounds bind to and activate taste cell GPCRs (G-protein-coupled receptors) that couple through the gustatory G-protein gustducin [10] to specific second messenger cascades [8–11]. Two families of taste receptors have been identified: T1Rs (type 1 taste GPCRs) include three members (T1R1, T1R2 and T1R3), while T2Rs (type 2 taste GPCRs) include 25–30 members and respond to bitter compounds [9]. Based on heterologous expression of taste receptors and behavioural assays of knockout mice, the combination T1R1 + T1R3 was identified as being responsible for mediating the ‘umami’ (Japanese for delicious) taste of glutamate and l-amino acids, whereas the T1R2 + T1R3 receptor combination was shown to function as a broad-specificity sweet sensor for natural sugars, sweet proteins and artificial sweeteners [8,9,12–17]. Key elements of taste transduction pathways are α, β and γ subunits of gustducin (α-gustducin, Gα [10,18], PLCβ2 (phospholipase Cβ [19] and TRPM5 (transient receptor potential melastatin 5) [20–22], a Ca2+-activated cation channel [23–26]. In the human intestine, the SGLT3 protein, a member of the sodium/glucose co-transporter family, has been proposed to be a glucose sensor and has been shown to be expressed in cholinergic neurons of the submucosal and myenteric plexus as well as in skeletal muscle at the neuromuscular junction [27]. Using in situ hybridization, we have shown that in mouse intestine, SGLT3 mRNA is also only expressed in cholinergic neurons and not in any of the cell-surface epithelial cells (J. Dyer and S.P. Shirazi-Beechey, unpublished work).

In considering these findings, with respect to the intestinal epithelium, α-gustducin was shown to be present in brush cells of the rat proximal intestine [28], in mouse intestinal endocrine cells and in a murine enteroendocrine cell line [29], suggesting that taste-sensing mechanisms may exist in the gastrointestinal tract. More recent evidence has now shown that the T1R family of receptors is present in rodent gut and the enteroendocrine STC-1 cell line [30]. Furthermore, it has...
been demonstrated that α-gustducin, T1R2, T1R3 and several other taste signalling elements are co-expressed in mouse and human enteroendocrine cells [31,32]. Collectively, these results reinforce the notion that the intestinal epithelium possesses receptors that are capable of ‘tasting’ the dietary composition of the luminal content and that the T1R2 + T1R3 receptor is a likely candidate for the role of luminal sugar sensor.

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

Convincing evidence for the involvement of the sweet taste receptor and gustducin in intestinal sweet taste transduction is provided by recent studies using mouse knockout mice lacking α-gustducin or the sweet taste receptor subunit, T1R3. Eliminating sweet taste transduction in mice in vivo by deletion of either the α-gustducin or T1R3 gene prevented the dietary sugar- and artificial sweetener-induced up-regulation of SGLT1 expression that was observed with wild-type mice [31]. In wild-type mice maintained on a high-carbohydrate diet (70% w/v sucrose), there was an approx. 2-fold increase in SGLT1 mRNA and protein abundance compared with mice fed an isocaloric low-carbohydrate (1.9% sucrose) diet [31]. This increase correlated quantitatively with an increase in the initial rate of Na+-dependent glucose transport into isolated brush-border membrane vesicles. There were no associated morphological changes in intestinal structure, determined by either measurements of crypt depths and villus heights, or by levels of the structural proteins β-actin and villin. T1R3- and α-gustducin-knockout mice, however, showed no change in SGLT1 mRNA, protein and function on either diet. The expression of SGLT1 in both types of knockout mice was identical with that of wild-type animals on the low-carbohydrate diet. 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 α-gustducin, that regulates SGLT1 expression in response to luminal sugars [31]. Therefore knocking out either α-gustducin or T1R3 abolishes the ability of mouse intestine to increase SGLT1 expression in response to increased dietary carbohydrate. Furthermore, artificial sweeteners that activate T1R2 + T1R3 in taste cells of the tongue, when included in the diet, also increased SGLT1 expression [31]. This indicates that the intestinal sugar sensor has similar sugar selectivity to that in the lingual epithelium. Furthermore, the data may explain in part the failure of artificially sweetened foods and beverages to lead to weight loss. The up-regulation of SGLT1 by these agents and the resultant increase in carbohydrate absorption from the diet, defeat attempts to lose weight.

**T1R2 + T1R3 and α-gustducin are expressed in enteroendocrine cells**

Using two complementary approaches, in situ hybridization and immunohistochemistry, SGLT1 was shown to be expressed in the enterocytes of the entire villus, and to be absent from the crypts [31]. T1Rs and α-gustducin, however, were expressed only in a subpopulation of villus cells, also containing chromogranin A (a specific enteroendocrine cell marker) [31]. The localization of α-gustducin to enteroendocrine cells has also been shown by other workers [29]. Moreover, a recent study by Jang et al. [32] has shown that the enteroendocrine cells that express T1R3 and α-gustducin also contain effector enzymes (including PLCβ2) and the TRPM5 channel known to function in taste transduction, suggesting that a similar transduction pathway to that in taste cells of the tongue may be operative in the intestinal enteroendocrine cells. Furthermore, using laser capture microdissection and RT (reverse transcriptase)–PCR, it was demonstrated that enteroendocrine L and K cells expressing the hormones GLP-1 (glucagon-like peptide 1) and GIP (glucagon-like insulinotropic peptide) respectively also contain α-gustducin, whereas captured enterocytes were devoid of α-gustducin [32]. Related to this, T1Rs and α-gustducin expression has been detected in murine enteroendocrine cell lines STC-1 [30] and GLUTag [31]; however, enterocyte cell line models, Caco2-TC7, IEC6 and FHs74, that expressed SGLT1 lacked T1Rs (J. Dyer and S.P. Shirazi-Beechey, unpublished work). Overall, this provides compelling evidence that T1R2 + T1R3, α-gustducin and other taste signalling elements are selectively expressed in enteroendocrine cells.

**Cellular location of SGLT1 and the sugar receptor suggests the existence of chemical signalling**

The fact that SGLT1 and gut-expressed taste receptors are in different cells has led to the proposal that a chemical signalling pathway exists between cells sensing the luminal sugar, i.e. the enteroendocrine cells, and those expressing SGLT1, i.e. the absorptive enterocytes [31]. In the lingual epithelium, type II taste receptor cells contain the detection and transduction machinery to respond to taste molecules; upon their activation, type II cells release ATP through hemichannels to activate type III taste receptor cells, which form conventional synapses with sensory nerve fibres [33–35]. The intestinal mucosal cells, however, are not in direct contact with the enteric nervous system [36]. It is proposed that to relay the chemosensory information in the intestine, gut hormones are secreted by enteroendocrine cells in response to sugar-induced sweet receptor activation. These hormones, in a paracrine manner, then induce expression of more SGLT1 in the neighbouring enterocytes [31]. This proposal is supported by a number of seminal observations. Candidate hormones, the incretins GLP-1 and GIP, as well as GLP-2, are co-expressed with T1R2 + T1R3 and α-gustducin in enteroendocrine cells [32]. Infusion of the intestinal lumen with glucose, galactose, fructose, 3-O-methyl-D-glucose or α-methyl D-glucose causes GIP and GLP-1 secretion in a number of mammalian species [37–39]. These sugars also increase SGLT1 expression when infused into the intestinal lumen [4,6,40]. The application of either GIP or GLP-2 to the serosal aspect
of the intestine has also been shown to increase SGLT1 expression [41,42]. GLP-2, however, is known to have a ‘trophic effect’, i.e. enhancing intestinal structure and growth [43,44]. Lack of structural changes in response to increased dietary carbohydrates or luminal sugars implies that GLP-2 may not be a direct effector of SGLT1 expression. Consistent with this are the findings of Brubaker et al. [44] who demonstrated that in mice injected with GLP-2 twice daily for 10 days, there was stimulation of growth of the small intestine, but no increase in SGLT1 expression determined by phlorizin-inhibitable glucose transport. Work using rodent and human enteroendocrine cell lines expressing T1R2+T1R3, α-gustducin and other taste signalling elements has shown that enhanced secretion of GLP-1 and GIP occurs with an increase in the artificial sweetener, sucralose, content of the cell culture media, and that hormone secretion is blocked by specific inhibitors of the sweet taste receptor [31,32]. It is suggested that the T1R2+T1R3 sweet taste receptor, expressed on the luminal membrane of villus enteroendocrine cells, senses the luminal glucose concentrations. Luminal glucose above a threshold level activates, in enteroendocrine sensor cells, a signalling pathway involving T1R2+T1R3, α-gustducin and other taste signalling elements, resulting in the secretion of GLP-1, GIP and/or other endocrine products. One or more of these hormones bind to receptors on their target cells and enhance SGLT1 expression [31]. It is possible that the chemical signals released by the enteroendocrine cells may be further transduced into intermediary neuronal signals (for example, with nerves located within the muscle and loose connective tissue underlying the epithelial layer). The neurons, in turn, would release cytokines that, directly or indirectly, act upon the enterocytes to enhance SGLT1 expression. Whatever the mechanism involved, signalling between cells is likely to require the presence of receptors on the basal membrane of target gut cells and their identification creates an exciting avenue for further research.

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

There is a wide variation in taste perception between different species and lineages of vertebrates. This is intimately related to their diet and environment [45]. Among birds, a characteristic response to sweet stimuli is absent in chicken [46], although a strong preference for sweet substances is well documented in hummingbirds and other nectar feeders [47]. Moreover, 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 [48]. Characterization of vertebrate genome sequences has shown that the T1R2 gene is absent in chicken and is an unexpressed pseudogene in cats [45,48]. In chicken and cats, however, T1R1 and T1R3, the umami-stimulated subunits, are expressed and functional, enabling them to taste glutamate, L-amino acids and proteins [48]. In consideration of these findings with respect to intestinal sugar sensing and SGLT1 up-regulation, it had been shown by Buddington et al. [49] that in cats the intestinal sugar transporter was unaffected by the feeding of a high-carbohydrate diet. They concluded that cats do not up-regulate SGLT1 expression in response to increased dietary carbohydrate levels [49]. Furthermore, Planas and co-workers [50] have reported that expression of SGLT1 in chicken intestine was unresponsive to increased luminal glucose. As each subunit of the heterodimeric T1R2+T1R3 sweet taste receptor is required for sweet-responsiveness, the loss of T1R2 in cats and chickens provides the genetic explanation for the lack of response of SGLT1 to changes in dietary carbohydrates in these species; these animals are incapable of detecting luminal sugars. It appears, therefore, that there is a link between the absence of T1R2 expression and the inability to increase SGLT1 in response to increased dietary sugar.

In recent years, there has been remarkable progress made towards understanding the mechanism of intestinal sugar sensing. The work described in the present review has added a wealth of evidence supporting the existence of an intestinal sugar receptor and outlining its role in glucose sensing and the subsequent modulation in expression of the intestinal glucose transporter. Considering the nutritional and clinical importance of intestinal glucose absorption, the involvement of the gut-expressed sweet taste receptor and gustducin in sensing dietary sugars and sweeteners, and effecting incretin hormone release from chemosensory enteroendocrine cells, makes them suitable targets for therapeutic modulation of the capacity of the gut to absorb sugars. This has implications for diet-related disorders, including diabetes and obesity, as well as the treatment of malabsorption syndromes.

References


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