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NONRUMINANT NUTRITION SYMPOSIUM: Intestinal glucose sensing and regulation of glucose absorption: Implications for swine nutrition[1]

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ABSTRACT: The Na^{+}/glucose cotransporter (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 and avoidance of intestinal malabsorption. This has important nutritional implications in particular for young and growing animals. It has been demonstrated that dietary sugars and artificial sweeteners increase SGLT1 expression and the capacity of the gut to absorb monosaccharides. Furthermore, diets supplemented with artificial sweeteners have been shown to improve growth and performance of weaning piglets. In this review, after describing the organization of intestinal epithelium, the type of gut hormones released in response to dietary carbohydrates, the mechanism underlying the transcellular transport of glucose in the intestine is outlined. Next, a historical background to the work carried out in various laboratories aimed at identifying molecular mechanisms involved in regulation of intestinal glucose transporter, SGLT1, is described. Subsequently, the more recent data on the role of intestinal glucose, or sweet, sensor T1R2 + T1R3, a G protein-coupled receptor, required for upregulation of SGLT1 by dietary sugars and artificial sweeteners, are presented. The glucose sensor subunits, T1R2 + T1R3, are members of the taste receptor family 1, T1R, and are expressed in the gut enteroendocrine cells. Sensing of dietary sugars and artificial sweeteners by T1R2 + T1R3 activates a pathway in endocrine cells leading to secretion of gut hormones. Finally, after describing molecular mechanisms by which a specific gut hormone released by endocrine cells may regulate SGLT1 expression in the neighboring absorptive enterocytes, the application of these findings to enhancing intestinal capacity to absorb dietary sugars in weaning piglets is presented. A better understanding of the molecular events involved in regulation of SGLT1 will allow the identification of nutritional targets with attendant promise of avoiding nutrient malabsorption and enhancing growth and well-being of species.

Key words: dietary additive, dietary carbohydrate, glucose absorption, glucose sensing, intestine, weaning piglet

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INTRODUCTION

Epithelial cells lining the inner surface of the intestinal epithelium are in intimate contact with a luminal environment that varies dramatically with diet. It has long been suggested that the endocrine "sensor" cells of the intestinal epithelium have detectors on the apical surface that can directly "taste" luminal nutrients and that these cells respond by releasing peptides (Furness et al., 1999). However, it is only recently that the nature of intestinal nutrient sensing molecules and underlying mechanisms has become available.

It is now known that there are several nutrient sensors expressed on the luminal membrane of endocrine cells that are activated by various dietary nutrients. The majority of these sensors are guanosine (**G**) pro-

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tein-coupled receptors. The accessibility of the nutrient sensors and the important role that they play in regulation of various functions of the gastrointestinal tract and gut-brain axis make them attractive nutritional and therapeutic targets for manipulation.

This review focuses on the nature of the intestinal glucose or sweet sensor and its role in regulation of intestinal glucose absorption. Effect of artificial sweeteners, included in diets of weaning piglets, on enhancing the capacity of the intestine to absorb dietary sugars will be highlighted. Understanding of molecular and cellular mechanisms regulating intestinal nutrient absorption allows the design of rational and innovative approaches to formulate feed and feed additives to ensure the health and well-being of the animal.

INTESTINAL EPITHELIUM

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 daughter cells that differentiate into several lineages. The epithelial cells consisting of polarized absorptive enterocytes, mucus-secreting goblet cells, enteroendocrine cells, and Paneth cells arise as descendents of these daughter cells (Cheng and Leblond, 1974). Paneth cells, which secrete antimicrobial peptides, digestive enzymes, and growth factors, complete their differentiation at the crypt base. The other 3 epithelial lineages differentiate during a highly organized upward migration from the crypt to the villus tip where they are extruded into the intestinal lumen. This process takes 2 to 3 d in the majority of species (Traber, 1990; Attaix and Meslin, 1991; Ferraris and Diamond, 1993).

Enterocytes constitute the majority (90%) of cells lining the villus. They are involved in vectorial transport of nutrients from the lumen of the intestine to the systemic system. These polarized cells possess 2 membrane domains: apical (i.e., brush border) and basolateral. These membranes differ in function, structure, and surface charges, 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 (Shirazi-Beechey et al., 1990).

Enteroendocrine cells, dispersed among the cells lining the intestinal epithelium, represent 1% of the cells. The majority have long, slender apical processes extending into the gut lumen (Figure 1). Enteroendocrine cells respond to changes in gut contents by releasing peptides. At least 20 different endocrine cell subpopulations have been defined based on their principal endocrine products. These gut peptides play critical roles in controlling various gastrointestinal functions and gut-brain communication (Rehfeld, 2004).

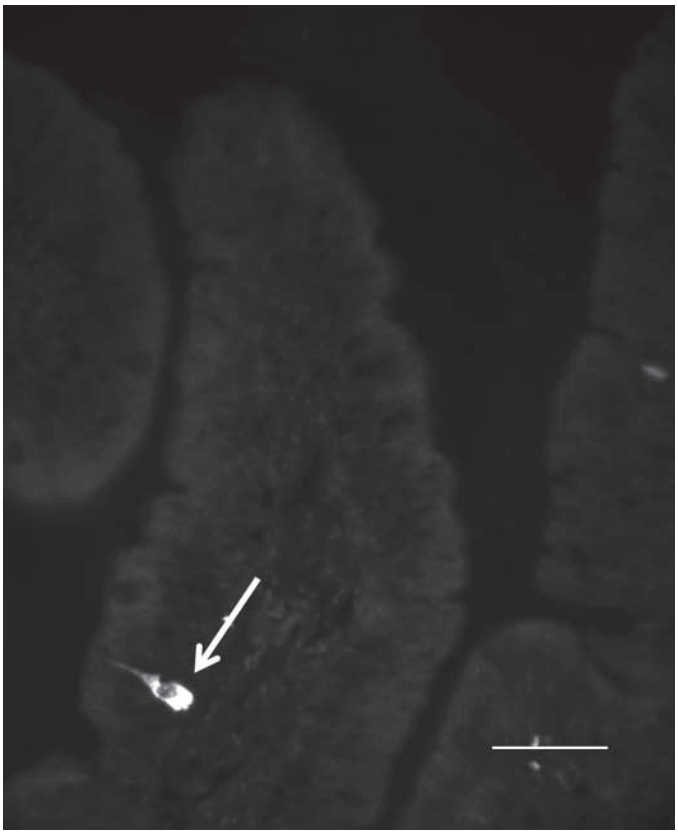

Figure 1. An intestinal villus with a typical flask-like-shaped enteroendocrine cell among the surface epithelial cells. Enteroendocrine cells have long, slender processes that extend to the gut lumen where they can detect the luminal contents. The villus is a section from the pig intestine, and the enteroendocrine cell is identified by immunohistochemistry using an antibody to chromogranin A. Scale bar represents 10 μm.

GUT HORMONES RELEASED IN RESPONSE TO DIETARY CARBOHYDRATES

Dietary carbohydrates stimulate the release of several gut peptides from the endocrine cells such as glucagon-like peptide (**GLP**)-1, GLP-2, glucose-dependent insulinotropic peptide (**GIP**), and serotonin. Dietary fats, bile acids, and short-chain fatty acids, such as propionate and butyrate, the latter produced by colonic microbial fermentation of dietary fiber, have also been reported to evoke GLP-1 release from endocrine cells of the small and the large intestine (Zhou et al., 2008; Thomas et al., 2009; Beglinger et al., 2010).

The gut hormones, GLP-1 and GLP-2, are released by endocrine L-cells, whereas K-cells secrete GIP (Ponter et al., 1991; Elliott et al., 1993). Endocrine L-cells are found scattered throughout the small and large intestine, with the greatest density in the distal ileum and colon (Eissele et al., 1992). However, L-cells have been identified at low density in the duodenum (Mortensen et al., 2003) and in greater numbers in the jejunum (Eissele et al., 1992). Endocrine K-cells are predominantly located in the duodenum. Interestingly, a proportion of cells in the proximal small intestine express both

GLP-1 and GIP (Mortensen et al., 2003; Theodorakis et al., 2006). Enterochromaffin cells, a subset of enteroendocrine cells, secrete serotonin in response to dietary carbohydrates. The number of enterochromaffin cells increases aborally (Sjölund et al., 1983). 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.

INTESTINAL GLUCOSE ABSORPTION

Dietary carbohydrates are hydrolyzed in the small intestine, by pancreatic amylase and brush-border membrane disaccharidases, to monosaccharides, glucose, galactose, and fructose. Mammalian cells can only transport monosaccharides. Glucose and galactose are transported across the apical membrane of enterocytes by Na^+/glucose cotransporter 1, **SGLT1** (Figure 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 (Shirazi-Beechey, 1995; Wright et al., 2007). Oral rehydration therapy relies on the ability of glucose to activate intestinal salt and water absorption via SGLT1 (Hirschhorn and Greenough, 1991). Fructose is transported by the 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 circulation by another Na^+-independent monosaccharide transporter, **GLUT2**, a bidirectional transporter that can move glucose out of or into the cell depending on its concentration gradient (Shirazi-Beechey, 1995). It has been shown that SGLT1 is expressed on the brush-border membrane of villus cells (Figure 2) in most mammalian species studied (Takata et al., 1992; Freeman et al., 1993; Margolskee et al., 2007; Dyer et al., 2009; Moran et al., 2010b; Batchelor et al., 2011). In general, expression levels are in the order of jejunum > duodenum > ileum. However, SGLT1 is not expressed in any epithelial cells (i.e., absorptive, endocrine, or goblet cells) of mammalian large intestine (Balen et al., 2008; Binder 2010). Furthermore, work in our laboratory has demonstrated expression of villin, a brush-border membrane marker, on the luminal membrane of colonic absorptive cells, and chromogranin A, a classical marker of endocrine cells, in colonic endocrine cells. However, there was no SGLT1 protein expressed either on the luminal membrane of colonocytes or in any endocrine cells of the large intestine (M. Al-Rammahi and S. P. Shirazi-Beechey, unpublished data).

It has been suggested by some workers that, in rat intestine in response to greater concentrations of luminal glucose or fructose, GLUT2 is trafficked to the luminal membrane of enterocytes where it can transport glucose and fructose (Kellett and Helliwell, 2000; Affleck et al., 2003). However, several approaches used by various investigators (Cui et al., 2005; Barone et al., 2009; Dyer et al., 2009; Moran et al., 2010b; Batchelor et al., 2011) have confirmed that GLUT2 only participates in the transport of monosaccharides across the basolateral membrane, where the protein is located exclusively. Therefore, it has been concluded that SGLT1 is the

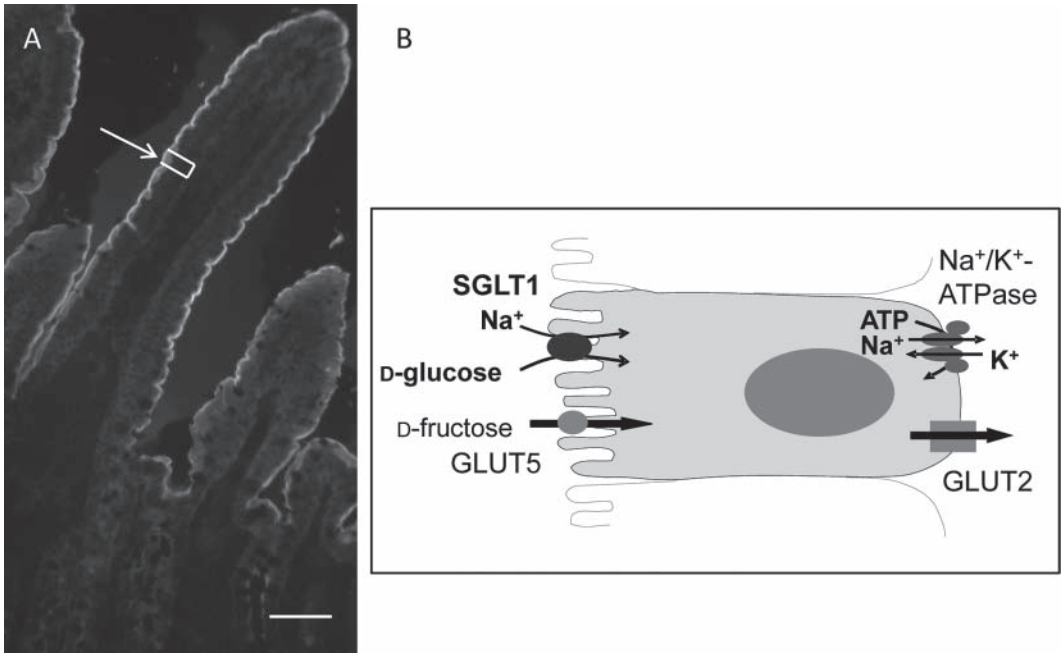

Figure 2. Panel A: A typical immunoflourescent image, showing Na^+/glucose cotransporter 1 (SGLT1) protein (white labeling) on the luminal membrane of epithelial cells along the villus. Scale bar represents 10 μm. Panel B: The boxed image showing a schematic diagram of an enterocyte with SGLT1 and fructose transporter (GLUT5) on the luminal membrane and the monosaccharide transporter (GLUT2) on the basal membrane.

major route for the absorption of dietary glucose from the lumen of the intestine into enterocytes.

REGULATION OF SGLT1: HISTORICAL BACKGROUND

Work in various laboratories has shown that in the majority of species (see exceptions discussed subsequently) monosaccharides in the lumen of the intestine directly regulate SGLT1 expression (Solberg and Diamond, 1987; Shirazi-Beechey et al., 1991a; Ferraris and Diamond, 1993; Dyer et al., 1997). Intestinal infusions with glucose or galactose (i.e., metabolizable substrates for SGLT1), α-methyl-glucose and 3-O-methyl glucose (i.e., nonmetabolizable substrates for SGLT1), and fructose (i.e., not a substrate for SGLT1) resulted in upregulation of SGLT1 expression, indicating that a wide range of monosaccharides are effective in enhancing expression of SGLT1 and that metabolism of sugar is not required (Solberg and Diamond, 1987; Shirazi-Beechey et al., 1991a; Lescale-Matys et al., 1993). The increase in expression was not accompanied by any changes in intestinal surface area for absorption (Shirazi-Beechey et al., 1991b). Furthermore, the introduction of membrane-impermeable glucose analogs to the lumen of the intestine also stimulated SGLT1 expression (Dyer et al., 2003). 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 analogs, however, had no inhibitory effect on Na^+-dependent glucose transport function, thereby ruling out SGLT1 as the glucose sensor. Further work using in vitro models indicated that sugar-mediated upregulation of SGLT1 is likely to involve a G-protein coupled second-messenger pathway (Dyer et al., 2003).

SWEET TASTE RECEPTOR OF LINGUAL EPITHELIUM

The sweet taste receptor expressed in taste cells of lingual epithelium is a heterodimer of taste receptor type 1, members 2 and 3, **T1R2 + T1R3**, subunits that couple through the gustatory G-protein gustducin (McLaughlin et al., 1992) to specific second messenger cascades. Based on heterologous expression of taste receptors and behavioral assays of transgenic (i.e., T1R2, T1R3, gustducin knockout) mice, the combination of T1R2 + T1R3 was shown to function as broad-specificity sweet sensor for natural sugars, sweet proteins, and artificial sweeteners (Montmayeur et al., 2001; Nelson et al., 2001). In the lingual epithelium, key elements of taste transduction pathways are the α-β and γ-subunits of gustducin, phospholipase Cβ2 and transient receptor potential melastatin 5, a Ca^{2+}-activated cation channel (Liu and Liman, 2003; Prawitt et al., 2003; Zhang et al., 2003).

INTESTINAL GLUCOSE SENSOR

With respect to the intestinal epithelium, α-gustducin was shown to be present in brush cells of rat proximal intestine (Höfer et al., 1999), in mouse intestinal endocrine cells, and in a murine endocrine cell line (Wu et al., 2002), indicating 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 (Dyer et al., 2005) and proposed that they function as the luminal sugar sensor to control SGLT1 expression in response to dietary sugars. Subsequently, we showed that T1R2, T1R3, and the α-subunit of gustducin are coexpressed in K- and L-endocrine cells in a wide range of species including humans, mice (Margolskee et al., 2007), dogs (Batchelor et al., 2011), and pigs (Moran et al., 2010a). In pig intestine, these glucose sensing elements are also expressed together in enterochromaffin cells containing 5HT. However, the enterochromaffin cells expressing T1R2, T1R3, and gustducin were few and far between compared with either L- or K-cells expressing these taste elements (10 vs. 50% respectively; Moran et al., 2010a).

Using GLUTag cell lines, derived from endocrine colonic tumors and primary cells, Parker et al. (2010) proposed that secretion of GLP-1 by L-cells and GIP by K-cells is through uptake of sugar by SGLT1; the secretion of these gut hormones was inhibited by the drug, phlorizin. Parker et al. (2010) suggested that SGLT1 is the likely mediator of the direct responsiveness of K- and L-cells to luminal sugars. It must be noted that phlorizin is a nonselective inhibitor of SGLT1 with a poor bioavailability because most of the drug is metabolized to phloretin, the aglycone of phlorizin (Mather and Pollock, 2010). In addition to inhibiting SGLT1 function, it affects many other processes including inhibition of the epithelial Cl^-/HCO_3^- exchanger (Cremaschi et al., 2001) and changes in signal transduction pathways (Jung et al., 2009). Furthermore, SGLT1 is not expressed in any epithelial cells of the colon (Balen et al., 2008; Binder, 2010) where there are ample GLP-1 secreting L-cells. These findings shed doubt on the role of SGLT1 as a glucose sensor that initiates gut hormone release. Further research is required to identify if there are any other sugar-sensing molecules expressed in the gut epithelium.

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 (i.e., knockout mice). Eliminating sweet taste transduction in mice in vivo by dele-

tion of either α-gustducin or T1R3 prevented dietary sugar- and artificial sweetener-induced upregulation of SGLT1 expression that was observed with wild-type mice (Dyer et al., 2007; Margolskee et al., 2007). In wild-type mice maintained on a high-carbohydrate diet (i.e., 70% sucrose, as fed), there was a 2-fold increase in the steady-state SGLT1 mRNA and protein abundance compared with mice fed an isocaloric low-carbohydrate (i.e., 1.9% sucrose, as fed) diet. This increase correlated quantitatively with an increase in the initial rate of Na^+-dependent glucose transport into isolated brush-border membrane vesicles. The 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 the mouse intestine to increase SGLT1 expression in response to increased dietary carbohydrate.

The expression of SGLT1 in T1R3 and gustducin knockout mice was identical to that of wild-type animals on the low carbohydrate diet (Dyer et al., 2007; Margolskee et al., 2007). This indicates that there is constitutive SGLT1 expression, independent of luminal sugar sensing by T1R3, α-gustducin, or both that maintains basal SGLT1 expression, and an inducible pathway, dependent on T1R3 and gustducin, that regulates SGLT1 expression in response to luminal sugars (Margolskee et al., 2007). In support of this, we have recently shown that when piglets were maintained on isocaloric diets containing increasing concentrations of carbohydrate (i.e., 7, 36, 53, or 60%, as fed), 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% (Moran et al., 2010b). Collectively, the data indicate that the intestine has the capacity to absorb glucose via the basal SGLT1, but this becomes limiting when dietary carbohydrate exceeds a certain amount.

SGLT1 EXPRESSION IS NOT RESPONSIVE TO DIETARY SUGAR IN NATURALLY OCCURRING T1R2 MUTANTS

Characterization of vertebrate genome sequences has shown that the T1R2 gene is absent in the chicken and is an unexpressed pseudogene in cats (Li et al., 2005; Shi and Zhang, 2006). Among birds, a characteristic response to sweet stimuli is absent in chickens (Halpern, 1962). Moreover, the domestic cat, as well as other members of the *Felidae* family of obligate carnivores, such as tigers and cheetahs, show no preference for and cannot taste sugars (Li et al., 2005). In consideration of these findings with respect to intestinal sugar sensing and SGLT1 upregulation, it has been shown that cats cannot upregulate SGLT1 expression in response to increased dietary carbohydrate (Buddington et al., 1991). Furthermore, it was reported that expression of SGLT1 in chicken intestine was unresponsive to increased luminal glucose (Barfull et al., 2002). Because both subunits of the heterodimeric T1R2 + T1R3 are 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 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.

REGULATION OF SGLT1 EXPRESSION IN RESPONSE TO ARTIFICIAL SWEETENERS

Work in our laboratory has shown that there is a 2-fold increase in SGLT1 mRNA, protein, and glucose transport function in the intestine of wild-type mice maintained on a low carbohydrate diet when sucralose is included in the drinking water compared with mice maintained on the same diet and consuming plain water. In contrast, in response to supplementation with sucralose, neither the gustducin nor the T1R3 knockout mice showed an increase in SGLT1 expression, indicating that T1R2 + T1R3 are involved in sensing the presence of artificial sweeteners, as well as sugars in the intestinal lumen (Margolskee et al., 2007). The responsiveness of the intestinal sugar/sweetener sensor in wild-type mice to various artificial sweeteners was similar to that of the receptor in taste cells of the tongue. Accordingly, the inclusion of saccharine and acesulfame K in the drinking water elicited a ~2-fold increase in SGLT1 expression, but there was no increase in response to aspartame. Unlike in humans, aspartame does not taste sweet to mice and does not stimulate mouse T1R2 + T1R3 (Nelson et al., 2001; Li et al., 2002). It appears, therefore, that in mouse intestine only those artificial sweeteners that activate the mouse lingual epithelium sweet taste receptor also lead to upregulation of intestinal SGLT1 (Dyer et al., 2007; Margolskee et al., 2007). Upregulation of SGLT1 by artificial sweeteners is not limited to rodents; sweeteners also enhance SGLT1 expression in piglet intestine (Moran et al., 2010a), as discussed subsequently.

PATHWAYS CONTROLLING SGLT1 REGULATION

There is an increasing body of evidence to support that the gut hormone GLP-2, when applied systematically, upregulates SGLT1 expression (Cheeseman, 1997; Ramsanahie et al., 2003; Cottrell et al., 2006). Although there is 1 study indicating that GIP is involved in enhancing SGLT1 expression (Singh et al., 2008), 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 the GLP-2 receptor is not expressed in any surface epithelial cells but is present in the enteric neurons (Bjerknes and Cheng, 2001; Baldassano et al., 2009). Work in our laboratory, using immunohistochemistry, has identified that GLP-2 and GIP receptors, but not the GLP-1 receptor, are expressed in enteric neurons of mouse and pig intestine (M. Al-Rammahi and S. P. Shirazi-Beechey, unpublished data). Our finding on the location of GLP-2 receptor is consistent with that reported in guinea pig ileum and mouse jejunum (Bjerknes and Cheng, 2001; Baldassano et al., 2009). The role of GIP in eliciting upregulation of SGLT1 is, however, doubtful. Wild-type and GIP receptor knockout mice, when maintained on a high carbohydrate diet, both showed a 2-fold increase in SGLT1 expression compared with their counterparts maintained on a low carbohydrate diet [M. Hosokawa, N. Harada (both from the University of Kyoto, Japan), and S. P. Shirazi-Beechey, unpublished data].

The experimental data indicate that the sweet receptor expressed on the luminal membrane of villus endocrine cells senses the luminal glucose concentration. Luminal glucose, above a threshold, activates a signaling pathway in endocrine cells involving T1R2 + T1R3, gustducin, and other signaling elements, resulting in the secretion of GLP-1, GLP-2, and GIP. We propose that the candidate gut hormone, likely to be GLP-2, binds to its receptor on the enteric neurons activating pathways involved in regulation of SGLT1 in the enterocytes. In support of this, Debnam (1985) showed that increased luminal glucose concentrations in the ileum result in upregulation of SGLT1 in more proximal small intestine (i.e., jejunum) and proposed the involvement of a neuronal reflex mechanism underlying SGLT1 upregulation. In addition, Sharp et al. (1996) have reported that upregulation of SGLT1 in response to high luminal glucose was only achieved in an intact mucosa, and not in isolated enterocytes, suggesting the involvement of the enteric nervous system. Further work is underway in our laboratory to identify the pathways by which sensing of sugar by the endocrine cells regulates SGLT1 in the neighboring enterocytes.

APPLICATION OF ARTIFICIAL SWEETENERS TO DIET OF PIGLETS

In an intensive livestock production system, a shorter suckling period allows more piglets to be born. However, this practice leads to several disorders, including nutrient malabsorption, resulting in diarrhea, malnutrition, and dehydration (Nabuurs et al., 1996; Nabuurs, 1998; Everts et al., 1999). The artificial sweetener, Sucram, a combination saccharin and neohesperidin dihydrochalcone (**NHDC**), is routinely included in Europe in the commercial feed of piglets. Saccharin and NHDC are the only artificial sweeteners thus far approved by the European Union for inclusion in animal feed (European Commission, 2010). Neohesperidin dihydrochalcone is a semi-natural sweetener that blocks the bitterness of saccharin. Although it has been shown that inclusion of Sucram in the feed of piglets may be effective in preventing postweaning enteric disorders and enhancing the growth and performance of early weaned piglets (Sterk et al., 2008), the molecular basis of this effect, until now, was unknown. We have shown that there is a ~2-fold increase in SGLT1 expression at the level of mRNA, protein, and function in the intestine of 28-d-old piglets when weaned onto a commercial wheat- and soybean-based swine diet containing Sucram compared with piglets fed the same diet lacking Sucram. Addition of saccharin and NHDC, individually or together, to the drinking water of piglets also resulted in the same magnitude of SGLT1 upregulation (Figure 3). This indicates that inclusion of artificial sweeteners, either to the diet or drinking water, enhances the capacity of the piglet intestine to absorb dietary sugars and water (Moran et al., 2010a).

Analysis of the gustatory behavior of pigs toward several artificial sweeteners, which taste sweet to human subjects, has led to the proposal that pigs can taste sodium saccharin, but may not taste NHDC (Glaser et al., 2000). However, comparison of the AA sequence of swine with that of human and mouse (the latter cannot taste NHDC) indicates that interactive residues for NHDC in pig T1R3 resemble those in human. Work is underway in our laboratory to assess the effect of other artificial sweeteners on SGLT1 expression in pig intestine.

It is evident that the design of new sweeteners requires a good knowledge of structural and sequential variations of the sweet receptor in different species. This will facilitate the appropriate use of sweeteners to enhance intestinal nutrient absorption with the attendant promise of preventing postweaning malabsorption.

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 sugar concentration. Luminal sugar, when above a threshold concentration, activates a signaling pathway in endocrine cells involving T1R2 + T1R3, gustducin, and other signaling 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. A good knowledge of sequential properties of the sweet receptor in the species of interest is required for the selection of appropriate sweeteners. Understanding of molecular and cellular mechanisms underlying these processes allows the design of rational approaches to feed formula-

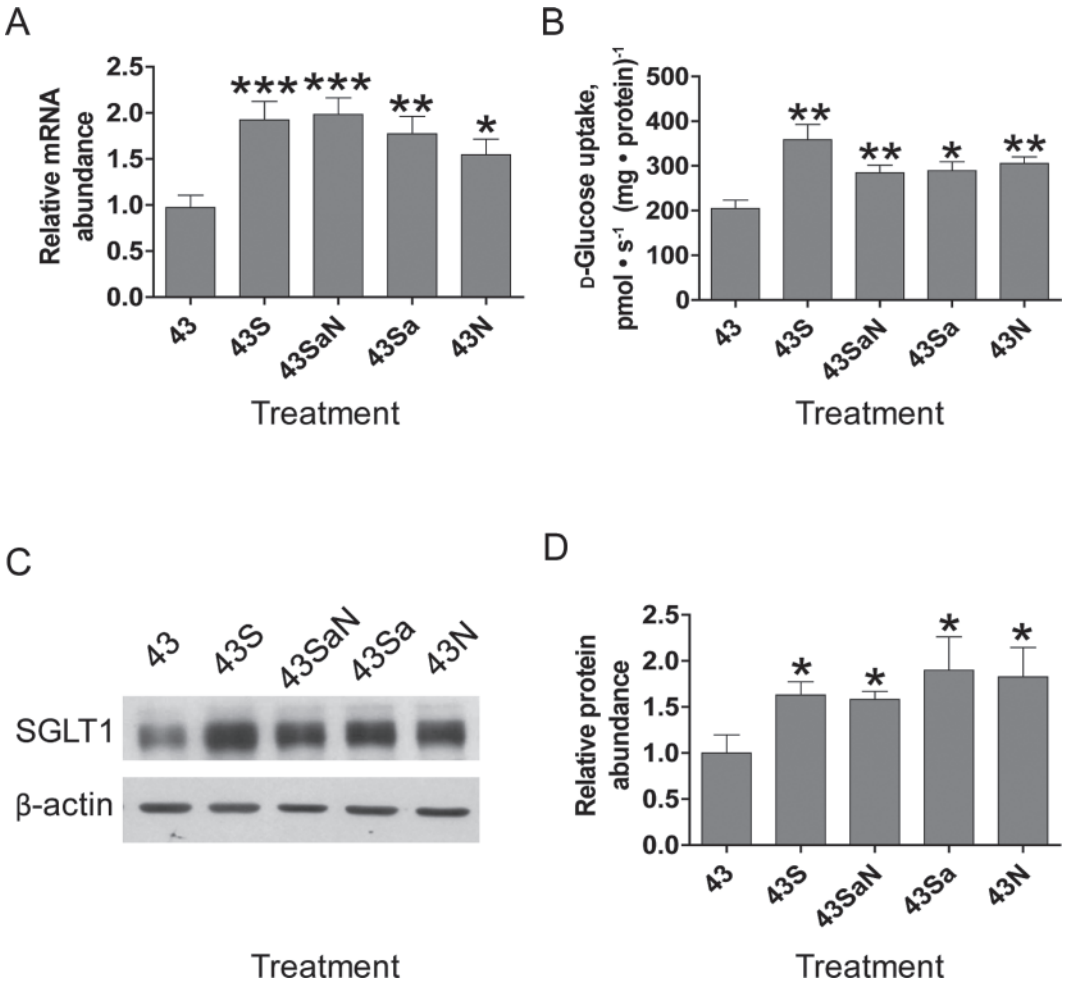

Figure 3. Expression of Na^+/glucose cotransporter 1 (SGLT1) in the small intestine of piglets in response to feeding them a commercial diet containing 43% carbohydrate, as fed (43), or supplemented with Sucram (43S), saccharin (43Sa), neohesperidin dihydrochalcone (NHDC; 43N), or saccharin and NHDC (43SaN). Panel A: Steady-state levels of SGLT1 mRNA abundance determined by quantitative PCR and normalized to β-actin mRNA. Panel B: Initial rates of Na^+-dependent D-glucose transport into brush-border membrane vesicles. Panel C: Abundance of SGLT1 protein measured by Western blot analysis. Panel D: Densitometric analyses of Western blots normalized SGLT1 protein expression to that of β-actin. Data were generated in triplicate with n = 6 to 12 animals per group. Results are shown as mean ± SEM. Statistically significant results determined using an unpaired Student's *t*-test are indicated by $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ (from Moran et al., 2010a, *British Journal of Nutrition* 104:637–646, ©Cambridge University Press).

tion and additives with the potential for the prevention of nutrient malabsorption and postweaning enteric disorders.

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