REVIEW ARTICLE

Dietary and developmental regulation of intestinal sugar transport

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The Na⁺-dependent glucose transporter SGLT1 and the facilitated fructose transporter GLUT5 absorb sugars from the intestinal lumen across the brush-border membrane into the cells. The activity of these transport systems is known to be regulated primarily by diet and development. The cloning of these transporters has led to a surge of studies on cellular mechanisms regulating intestinal sugar transport. However, the small intestine can be a difficult organ to study, because its cells are continuously differentiating along the villus, and because the function of absorptive cells depends on both their state of maturity and their location along the villus axis. In this review, I describe the typical patterns of regulation of transport activity by dietary carbohydrate, Na⁺ and fibre, how these patterns are influenced by circadian rhythms, and how they vary in different species and during development. I then describe the molecular mechanisms underlying these regulatory patterns. The expression of these transporters is tightly linked to the villus architecture; hence, I also review the regulatory processes occurring along the crypt-villus axis. Regulation of glucose transport by diet may

involve increased transcription of SGLT1 mainly in crypt cells. As cells migrate to the villus, the mRNA is degraded, and transporter proteins are then inserted into the membrane, leading to increases in glucose transport about a day after an increase in carbohydrate levels. In the SGLT1 model, transport activity in villus cells cannot be modulated by diet. In contrast, GLUT5 regulation by the diet seems to involve *de novo* synthesis of GLUT5 mRNA and protein in cells lining the villus, leading to increases in fructose transport a few hours after consumption of diets containing fructose. In the GLUT5 model, transport activity can be reprogrammed in mature enterocytes lining the villus column. Innovative experimental approaches are needed to increase our understanding of sugar transport regulation in the small intestine. I close by suggesting specific areas of research that may yield important information about this interesting, but difficult, topic.

Key words: fructose, glucose, GLUT5, metabolic regulation, SGLT1.

INTRODUCTION

The rate of absorption and the intestinal region where sugars are absorbed affect the time course of appearance of sugars in the blood, and the availability of those sugars to other parts of the body. Absorptive systems in the small intestine therefore influence plasma sugar concentrations and play a vital role in nutrition. Increasing our understanding of these absorptive systems may enhance our understanding of sugar metabolism.

In past reviews [1–3], I have alluded to the fact that studies on regulation of nutrient transport have often lagged behind those that determine mechanisms of transport. However, the number of studies on regulation of nutrient transport has increased markedly, and the purpose of this review is to summarize these recent studies and to suggest directions where future efforts can be focused. Recent related reviews on regulation include those of Shirazi-Beechey [4], Wright and co-workers [5], Corpe and co-workers [6] and Kellett [7].

Intestinal sugar transporters are responsible for transporting the monosaccharides glucose, galactose and fructose from the intestinal lumen to the blood. SGLT1 is located in the brush-border or apical membrane, and transports glucose and galactose, along with Na⁺, from the intestinal lumen into the cytosol. GLUT5 is also apical, a unique member of the ubiquitous facilitative glucose transporter family, and transports fructose from the lumen into the cytosol. GLUT2 is basolateral and

transports all three monosaccharides from the cytosol to the blood. In this review, I direct our attention to intestinal brush-border sugar transport. Both intestinal sugar transporters were cloned in the late 1980s or early 1990s [8–10], events leading to a decade of studies on molecular mechanisms regulating intestinal sugar transport. Reviews by Barrett et al. [11] and Wright and colleagues [12,13] relate physiological function to the molecular structure of these transporters.

We study regulation because it increases our understanding of mechanisms that ultimately lead to changes in rates of intestinal absorption of sugars. This is important, because intestinal sugar absorptive capacity is not present in substantial excess as is often assumed, but instead is matched to physiological demands [14], with capacity modestly exceeding demand by a safety factor of 2 [15]. For example, absorptive capacity is actually limiting in developing animals, because of the scarcity of certain transporters [16]. The benefits of safety factors that allow absorption when luminal sugar concentrations change rapidly must be balanced against the costs of transporter synthesis and limited membrane space. Secondly, absorption is limited in some disease states, such as post-gastrectomy malabsorption syndrome and short-bowel syndrome. Thirdly, sugar absorption increases under physiological conditions, such as hypothermia, hyperphagia, pregnancy, lactation and chronic consumption of high-carbohydrate diets [3], implying that the intestine's absorptive capacity is not infinite, and might be exceeded under these physiological

Abbreviations used: HNF-1, hepatocyte nuclear factor 1; MLTF/USF, major late transcription factor/upstream stimulatory factor.

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Figure 1 Intestinal absorptive cells or enterocytes are found on structures called villi (singular: villus) in the small intestine

Enterocytes arise from stem cells in the crypt region, then migrate upwards along the sides of the villus. Upward migration apparently occurs simultaneously with differentiation, because cells not only acquire new structures (e.g. more and longer microvilli), but also new absorptive functions as they migrate. The Na^+ -dependent glucose transporter SGLT1 and the Na^+ -independent fructose transporter GLUT5 proteins are located in the brush-border membrane of enterocytes that are sufficiently differentiated, mainly along the middle and upper villus regions. Hence, regulation of intestinal absorptive function *in vivo* is invariably linked to villus architecture. Because enterocytes are exposed to intestinal luminal enzymes, they are easily damaged. Extrusion of damaged cells occurs near the tip of the villus, about 2–3 days after the cells emerge from the crypt.

conditions were it not for adaptive increases in absorption rates. Fourthly, the rate and site of absorption of a nutrient determine the time course of post-prandial changes in that nutrient's concentrations in the plasma. Hence it is important to understand intestinal adaptations that alter nutrient absorption rates, and therefore post-prandial plasma nutrient concentrations.

In this review, I exclude most studies on regulation of sugar transport in oocytes and cell cultures, not only because regulation sometimes differs among and within cell lines themselves [17], but also because regulation in cell culture sometimes differs from that observed *in vivo* and in isolated intestinal tissues. For example, in fully differentiated Caco-2/TC7 cells, thyroxine and glucose clearly increase GLUT5 mRNA abundance in a dose-dependent manner [18]. In rat intestine, however, changes in dietary glucose [19,20] and plasma thyroxine [21] concentrations have no effect on either GLUT5 mRNA and protein abundance or fructose transport. Moreover, an intact mucosa is necessary for rapid up-regulation of glucose transporters by luminal glucose [22]. Nonetheless, important experiments, such as identification of critical sequences in the promoter region of transporter genes, can only be performed using these cells [18,23,24].

With few exceptions, I also exclude the large number of studies on changes in sugar transport as effected by hormones and growth factors (e.g. [25–28]), or by fasting and starvation [29]. I review specific changes in sugar transport rate per cell, per mg of protein or per weight of intestine, and not non-specific changes that alter mucosal mass or cell number, leading to non-specific changes in transport of all nutrients. Specific changes in sugar-transport rate are often those induced during ontogenesis or by changes in the diet [3].

The small intestine is a difficult organ system to study. One reason is that intestinal absorptive cells are polar: the protein and lipid composition of apical membranes facing the food side differ from those of basolateral membranes facing the blood side (Figure 1). Polarity of cells allows the efficient transfer of sugars from the intestinal lumen to the blood. Another reason is that the function of these cells changes, depending on whether they are 'young' or 'old', and where they are along the villus. Relative to most other cells in the body, intestinal cells have a short life span. They arise from stem cells in the crypts, then undergo differentiation as they migrate towards the villus tip, where they are eventually exfoliated 2–5 days after emerging from the crypt (life span depends mainly on species and intestinal region; see Figure 1). Many nutrient transporters are found only in the apical membrane of mature cells along the villus, and not in cells lining the crypt. This age-dependent or location-dependent expression of transporters cannot be reproduced in any culture system lacking a well-defined villus architecture.

SGLT1

SGLT1 is a high-affinity glucose transporter that is found in both small intestine and kidney [30]. Although transport measurements and ligand-binding experiments suggest the presence of more than one type of Na^+ -dependent glucose transport system in the small intestine, so far only SGLT1 has been found. The absence of functional SGLT1 in the intestinal brush-border of humans with glucose–galactose malabsorption is probably the most crucial evidence demonstrating the importance of this protein in absorption of dietary glucose and galactose [12,31].

I now describe how intestinal glucose transport mediated by this system is regulated by diet and circadian rhythm, and during development. I will initially describe the patterns of changes in SGLT1 mRNA, protein and activity, then describe the mechanisms underlying these changes.

Effect of diet

Carbohydrate levels and composition

There seem to be two distinct time scales of dietary regulation of glucose transport. In rats, mice and sheep, intestinal glucose transport increases in about 1–3 days after a switch to a high-carbohydrate diet [32–34]. The time course of increase in transporter activity is similar to the time course of increases in site density of glucose transporters [33,35], and in levels of SGLT1 mRNA [36]. However, glucose transporters can also respond to a change in intestinal luminal glucose concentration within ≈ 1 h [22]. Because intestinal glucose transport is also subject to diurnal rhythm [37], distinguishing short- and long-term dietary regulation from each other and from circadian regulation is a complicated task awaiting future study. In this section, I focus mainly on longer-term changes induced by dietary carbohydrate. The short-term regulation of SGLT1 expressed in *Xenopus laevis* oocytes was reviewed by Wright and co-workers [5].

Chronic consumption of high-carbohydrate diets typically leads to increases in rates of intestinal glucose transport. Recent studies in rats and mice have shown a similar trend [15,38], but many of the recent studies have provided newer perspectives on regulation of glucose transport by determining the effects of dietary carbohydrate on glucose transport in non-mammalian species, by determining the effects of other dietary constituents on glucose transport, or by simultaneously measuring levels of SGLT1 transport activity, protein and/or mRNA. Changes in glucose transport induced by alterations in dietary carbohydrate are highly correlated with changes in amounts of SGLT1 protein or in the number of specific phlorizin (a competitive inhibitor of brush-border glucose transport)-binding sites [39,40]. In contrast, the magnitude of diet-induced changes in SGLT1 mRNA abundance is typically less than that of changes in SGLT1 protein abundance, number of specific phlorizin sites or glucose transport rates. For example, the sheep small intestine, which normally does not have glucose in the lumen, does not express SGLT1 protein or mRNA. However, intestinal luminal, but not intravenous, infusion of glucose induces a marked increase in SGLT1 activity and protein abundance, but not in mRNA abundance [41,42], suggesting that dietary regulation of SGLT1 expression may be modulated mainly by translational or post-translational mechanisms. SGLT1 induction in sheep intestine can be initiated by transportable, but non-metabolizable, substrates of SGLT1, and even by non-transportable analogues, such as 2-deoxy-D-glucose [42]. Compared with those fed on low-carbohydrate or carbohydrate-free diets, SGLT1 mRNA abundance increases in rats fed on high glucose, galactose, glycerol, fructose, α -methyl glucose, 3-O-methyl glucose, xylose, mannose or sucrose diets [36,43]. These findings parallel those observed in the small intestine of mice, where glucose transport increases in response to glucose, galactose, 3-O-methyl glucose, fructose and maltose diets [44]. Either there is a variety of receptors for these signals inducing SGLT1, or there is a single receptor with a wide range of specificity for a variety of signals. In sharp contrast, GLUT5 expression is enhanced only by diets containing its substrate, fructose (see below).

SGLT1 in the human small intestine may also be regulated by diet [45]. Glucose transport was greater in brush-border membrane vesicles obtained from normal intestinal tissues exposed to

luminal nutrients than in vesicles obtained from adjacent dysfunctional tissues with limited exposure to luminal nutrients. This decrease in transport was due to specific decreases in amounts of SGLT1 protein, and was independent of differences in villus morphology.

Comparative aspects of regulation

Intestinal glucose transport increases with dietary carbohydrate in tilapia and catfish, findings that parallel earlier studies in various fish species, except for rainbow trout [46]. The changes are specific: in the case of tilapia, brush-border transport of other nutrients do not change with diet, while in the catfish, basolateral transport of glucose is not altered. Fish that regulate their glucose transport tend to be omnivores (e.g. catfish, tilapia) or herbivores (carp); carnivores like trout do not regulate. Omnivorous tadpoles regulate glucose transport [47], but when those same tadpoles metamorphose into carnivorous frogs, the ability to regulate glucose transport is lost. These results indicate that dietary adaptation of intestinal glucose transport is common among vertebrates, but is influenced by the potential variation of the carbohydrate content of the natural diet. Intestinal glucose transport in fish is likely to be mediated by SGLT1 for two reasons: phlorizin inhibits intestinal glucose transport in Antarctic fish [48], and SGLT1 mRNA is found in rainbow trout [49].

In contrast with dietary regulation of intestinal glucose transport in mammals, amphibians and fish, intestinal glucose transport does not change with dietary carbohydrate in most birds. This is interesting, because the diets of many birds change with seasons, and the levels of carbohydrate in those diets also vary with season. Nevertheless, intestinal glucose transport rates do not vary with dietary carbohydrate levels in American robins [50], house sparrows [51] and yellow-rumped warblers [52]. The absence of dietary modulation of glucose transport in birds may be due to the predominance of passive glucose transport, probably occurring through the paracellular pathway [51,53]. If transport were largely passive and dependent on transepithelial concentration gradients, then there would not be any need for specific changes in carrier-mediated transport [3]. For example, passive absorption of nutrients such as fat-soluble vitamins is not subject to modulation by diet [1].

Over-reliance on the passive pathway provides metabolic advantages and ecological constraints [54]. It does provide birds with an absorptive process that can deal with rapid and acute changes in luminal sugar concentrations. The passive pathway is also energetically inexpensive to maintain and modulate. However, passive absorption through the paracellular pathway is dependent mainly on concentration gradients, molecular sizes and charge. In the absence of a transport system that selects which luminal substrate to absorb, this non-discriminatory pathway may increase vulnerability to toxins, and thus constrain foraging behaviour and limit the breadth of the dietary niche of the birds [54]. Another problem is that when luminal sugar concentrations are lower than those in plasma, glucose may diffuse back into the lumen.

SGLT1 mRNA and activity were observed in the forestomach of ruminants such as cows and sheep, as well as in the intestine of cows [55–57]. Although dietary adaptation was not investigated, these findings are interesting, because intraluminal carbohydrates are thought to be completely converted into short-chain fatty acids by symbiotic micro-organisms in the gastrointestinal tract of ruminants. The absence of intraluminal carbohydrate removes the main signal for SGLT1 synthesis, hence post-weaning lambs lose intestinal SGLT1 as they progress from a

milk to a grass diet [41]. However, in domestic cattle consuming high amounts of cereal grain, up to 50% of the starch may escape fermentation [58]. Under these conditions, increases in SGLT1 expression are adaptive.

Effects of changes in levels of other dietary constituents

Sodium concentration. SGLT1 activity is clearly modulated by its substrate glucose so that intestinal glucose transport varies with intestinal luminal glucose (or dietary carbohydrate) concentrations. Is SGLT1 also modulated by dietary concentrations of its other substrate, Na^+ ? It has been established that low-salt diets decrease the V_{max} of intestinal glucose transport in chickens [59] by decreasing the number of brush-border glucose transporters, as measured by specific phlorizin binding [60] or Western blots [61]. The time course of regulation by dietary Na^+ is similar to that of regulation by dietary carbohydrate. Sodium depletion reduces intestinal glucose transport within a day after consumption of a low-salt diet, and the decrease reaches a maximum within 2 days [62]. The effect of high- Na^+ diets is limited to the small intestine, as dietary Na^+ has no effect on glucose transport rates and SGLT1 protein levels in the chicken colon [63]. The new finding that NaCl consumption modulates intestinal glucose transport suggests that chronic increases in luminal concentrations of both co-transported substrates of SGLT1 will lead to increased expression of this protein. It also suggests that certain elements in the SGLT1 promoter respond directly or indirectly via cofactors to changes in the salt content of the diet. It is not known whether the carbohydrate and Na^+ effects are additive, but this should be easy to test in animals fed a high-carbohydrate and high-salt diet. It is also not known whether the regulatory site(s) is/are specific to changes in the concentration of Na^+ or Cl^- , or whether other cations can substitute for dietary Na^+ .

There might also be a short-term time scale of regulation by dietary Na^+ , just as there is a short-term regulation by dietary carbohydrate. Four hours after drinking 150 mM NaCl, intestinal glucose transport increased markedly in chickens previously fed a low-salt diet, and glucose-uptake rates equalled those in chickens consuming a high-salt diet [64]. This rapid response suggests that the target of regulatory signals are mature enterocytes.

Fibre. In developed countries where obesity is a major health problem, there is an increasing need to identify low-energy bulk ingredients that decrease the caloric density of foods. The variety of low-energy, low-digestibility bulk ingredients can be enormous, and 'fibre' has been used as an all-inclusive term to include not only plant fibre, but also synthetic polysaccharides and indigestible animal by-products, such as chitin and other aminopolysaccharides. Insoluble fibres, such as cellulose and lignin, act as laxatives to accelerate the transit of luminal contents in the colon. Soluble fibres like bran and guar gum form viscous solutions and act mainly to delay gastric emptying. In an earlier review [3], I noted that a majority of studies on the effects of fibre on glucose transport did report a decrease in intestinal glucose transport with increasing fibre content. However, several studies also observed that fibre either had no effect on, or even led to an increase in, intestinal glucose transport.

Recent studies have been as inconclusive as previous ones. SGLT1 mRNA abundance and intestinal glucose transport rate in rats fed for 2 weeks on a diet containing highly fermentable fibre were similar to those fed on a diet containing less fermentable fibre [38]. In dogs, however, chronic consumption of a diet containing highly fermentable fibres increased total intestinal

absorption of glucose, mainly because this diet increased intestinal mass and surface area [65]. There were no specific increases in transport rate expressed per mg of tissue. In rats fed on high-molecular-mass dextrans, which are poorly digested carbohydrates, intestinal glucose transport increased [66].

Because dietary fibre tends to dilute the carbohydrate and sugar content of foods, its effect may be secondary to a decrease in intestinal luminal carbohydrate concentrations, so that intestinal glucose transport ultimately decreases. These conflicting reports may occur because the amount of fibre added to the experimental diets may be a small fraction of its total carbohydrate content, and does not lead to marked changes in carbohydrate concentration [3]. Moreover, dietary fibre also affects intestinal motility, mass and length, alters enterocyte migration rate, life span and turnover, and changes microbial metabolism, density and species. These changes may confound the specific effects of fibre, if any, on intestinal glucose transport.

Circadian rhythm

Intestinal glucose transport follows a distinct circadian rhythm [67]. This rhythm persists in starved rats, but is eventually lost in rats fed by continuous infusion for 9 days. Although rats do not eat during mid-afternoons, intestinal glucose transport nevertheless doubles at this time of day before gradually decreasing at night [37] when food consumption increases [68]. SGLT-1 mRNA and protein levels also increase in parallel with glucose transport [69,70]. Hence daily increases in SGLT1 expression do not occur at the same time as increases in food intake. Regulation of the circadian rhythm of glucose transport seems to occur independently of dietary regulation, so that there are at least two distinct and separate pathways regulating SGLT-1 expression and function in intestinal epithelial cells. One pathway utilizes gut luminal signals, such as those arising from a chronic change in dietary carbohydrate levels, as described above, to induce long-term changes in transport rates. The other pathway is a daily anticipatory mechanism preparing the intestine for an expected increase in amount of luminal contents [37]. This second pathway, however, need not be independent of the luminal glucose concentrations. The rhythmic expression of SGLT1 message and function may still be linked to the diurnal changes in luminal glucose concentration, even if the daily peak in rate of intestinal glucose uptake is out of phase with the daily peak in luminal glucose concentration. Intestinal luminal glucose concentrations in rats fed 65% (w/w) glucose pellets vary from 5 mM in late afternoons to almost 100 mM in the evening hours [68]. If the timing of the peak luminal glucose concentration were to be shifted to a later time, this shift may alter the timing of peak SGLT1 expression.

Development of transport

During ontogenetic development, specific changes in glucose transport normalized to tissue mass or protein are often masked by striking increases in mucosal mass and surface area. The fetal small intestine of many mammals, including humans [71], is known to actively transport glucose (for reviews, see [3,72]) or to express SGLT1 and GLUT2 mRNA at significant levels [73,74], as illustrated in Figure 2. Brush-border glucose transport gradually increases with gestational age. In rabbits, active uptake of glucose and galactose is increased 3-fold during the final 7 days of gestation [75]. Transport rate is typically highest straight after birth, but then decreases gradually thereafter. More recent studies in mink, rat and chicken confirm these findings [76–79].

Although glucose transport in adult rats can be regulated by diet, glucose transport does not change in neonatal (particularly

Figure 2 Schematic diagram depicting the initial appearance of rat intestinal sugar transporters during development

The continuous blue horizontal line represents the age of rats in days, and the various stages of development from gestation to weaning. GLUT2 and SGLT1 appear well before birth, during the early gestation period. The rat pup is totally dependent on dam's nutrition during the suckling phase occurring between 0 and 14 or 15 days. Pups begin to wean at day 15, after the suckling phase is completed. Pups can subsist solely on solid food, without losing body weight, from day 28 or later. Under normal conditions, GLUT5 appears very late during ontogenetic development; only insignificant amounts of GLUT5 mRNA and modest rates of fructose transport are observed before day 28. Precocious consumption (green arrows) of dietary fructose during the weaning phase rapidly enhances GLUT5 expression in the small intestine.

suckling) rats fed on high-carbohydrate pellets or neonatal rats whose intestines were perfused with high-glucose solutions [20,80,81]. Moreover, intestinal glucose transport is similar between adrenalectomized and sham-operated rat pups [82], and between hypothyroid and euthyroid rat pups [21]. The plasma concentrations of corticosterone, the hormone removed by adrenalectomy, and thyroxine increase markedly during weaning in rats. These endocrine factors regulate the development of intestinal brush-border enzymes during weaning [83], but apparently do not regulate the development of intestinal glucose transporters. The absence of regulation of glucose transport in rat pups that nurse on milk is consistent with earlier findings that glucose transport does not change in animals consuming a diet that does not vary in carbohydrate composition. However, intestinal cell turnover is very slow in suckling rats (> 7 day transit time from crypt to villus) [84]. It is possible that SGLT1 in cells present in the small intestine since birth cannot be regulated, and dietary regulation begins only when these cells are eventually replaced.

Further development of glucose transport in post-weaning rats (> 28 days of age) is thought to be 'hard-wired', and occurs independently of luminal cues. Decreases in the intestinal glucose transport rate are observed in both experimental rats weaned on to a 'milk replacer' diet and in control rats weaned on to a chow diet [16]. In sharp contrast, dietary substrates in lamb intestine can act as signals that trigger the developmental appearance of glucose transport (see review [4]). Lambs kept on a milk replacer diet are able to maintain high rates of intestinal glucose transport, whereas lambs weaned on to a grass diet show a marked decrease in transport [85]. It is not clear why changes in glucose transport during weaning are substrate-dependent in lambs but not in rats. The normal decrease in glucose transport rate in lambs is directly proportional to a decrease in abundance of SGLT1 protein [40], but is not correlated with a decrease in abundance of SGLT1 mRNA [41]. Whereas functional activity

and protein levels decrease by two orders of magnitude, mRNA levels decrease only 4-fold.

Glucose transport decreases modestly in the distal regions of the rat small intestine, and this proximal-to-distal gradient in transport becomes steeper with age [16,80]. There is also a proximal-to-distal gradient in SGLT1 mRNA abundance [86], but the gradient disappears in older rat pups. Hence patterns of regional distribution and of dietary regulation differ between SGLT1 mRNA abundance and rates of intestinal glucose transport.

Mechanisms underlying regulation

In order for intestinal transport to increase, a greater number of SGLT1 transporters must be inserted into the apical membrane. However, intestinal glucose transport activity and SGLT1 protein are typically found only in mature cells located in the upper villus regions [87–91], indicating that transporters are inserted during the cell's transition from the crypt to the villus. Long-term regulation of intestinal glucose transport occurring over several hours and days cannot be dissociated from regulation of glucose transport along the villus axis. The 12–24 h time lag between switching a mouse on to a high-carbohydrate diet and the initial appearance of enhanced glucose transport is consistent with two alternative hypotheses. Does substrate-dependent regulation of SGLT1 occur mainly in young cells in the lower villus regions or crypt, or can transport activity be reprogrammed in mature enterocytes? According to the first hypothesis, induction would be rapid and the lag would be due to cell migration times. By the second hypothesis, the lag would be due to induction itself. Diets containing different amounts of carbohydrate, but containing a sufficient amount of protein and essential amino acids, do not alter the cell migration rate [92]. It transpires that diet-induced changes in site density of glucose transporters initially appeared only in lower villus cells before spreading, over the

Figure 3 Determining the site density of glucose transporters at brief time intervals after a diet switch would distinguish between two hypotheses: induction of transporters in young cells in the lower villus or induction of transporters in cells of all ages

Graphs show the site density of glucose transporters along the villus axis at time t after a switch in levels of dietary carbohydrate, divided by site density before the switch ($t = 0$). In the upper panel, mice were switched from a carbohydrate-free to a high carbohydrate diet, then killed at time t . Note that in cells from the lower villus, transporter site density increased 12 h after the switch and stayed high thereafter. In cells from the tip, transporter site density increased only after 36 h. In the lower panel, mice were switched from a high-carbohydrate to a carbohydrate-free diet. Here, changes in site density also proceed with time from lower villus to mid-villus to upper villus to villus tips. Modified from Ferraris and Diamond [33], with permission. © (1992) The American Physiological Society.

course of several days, to the villus tips (Figures 1 and 3) [33,35]. There seemed to be two types of transporters distinguished by their phlorizin binding kinetics, with the site having the higher phlorizin affinity residing in cells from mid-villus to villus tip and accounting for most of the specifically bound phlorizin.

Sheep intestines normally do not transport glucose, and mature enterocytes along the villus do not express SGLT1 protein even when intestines have been infused with glucose solutions for 2 h. However, when sheep were fed on a glucose diet and killed 4 days later, functional SGLT1 was detected in the newly formed mature enterocytes [34]. In fact, if intestinal glucose or galactose transport were enhanced by chronic injections of retinyl palmitate or glucagon in rats, only glucose or galactose uptake by brush-border membrane vesicles from upper and mid-villus cells increased, after a time lag of several days after the first injection [93,94]. Hence young intestinal cells in the crypt of mouse and sheep intestine are apparently programmed irreversibly by the dietary carbohydrate level, and are not subsequently re-programmed during their lifetimes as they migrate up the villus (Figure 4).

Glucose transport activity and brush-border SGLT1 protein, but not SGLT1 mRNA, are found mainly in cells along the villus regions. In rats and rabbits, SGLT1 mRNA levels are low in the crypt, mid-villus and upper villus regions, and the greatest amount of mRNA is located in the crypt–villus junction [95–97]. This disparity in crypt–villus site of abundance of SGLT1 mRNA and protein parallel that of developmental studies, indicating quantitative differences between SGLT1 mRNA abundance and glucose transport rates [41]. Hence SGLT1-mediated glucose transport is likely to be mediated by post-transcriptional mechanisms. However, it is possible that dietary carbohydrate enhances transcription of SGLT1 in cells along the crypt or crypt–villus junction, and those cells will translate the message as they migrate up the villus column. SGLT1 mRNA abundance then decreases in upper villus cells, where the mRNA may be degraded (Figure 4). In fact, high-carbohydrate diets have been shown to increase the total abundance of SGLT1 mRNA in rat intestine by diet-induced increases in transcription rate [36]. However, the crypt–villus site of the diet-induced increase in both rate of transcription and mRNA abundance is not known. It is interesting to note that total intestinal SGLT1 protein and mRNA increase in streptozotocin-diabetic rats, and the diabetes-induced increase in mRNA abundance is confined to cells in the crypt and lower villus regions [98].

In contrast with observed changes in crypt–villus location of SGLT1 mRNA, such as those caused by diabetes and diet, levels of SGLT1 mRNA increase along the entire crypt–villus axis of intestines from rats killed in the afternoon and early evening [37]. The timing of this increase is similar to that of the circadian-related increase in SGLT1 mRNA abundance of the entire small intestine. These increases are preceded by marked increases in transcription rate of SGLT1 in the late morning hours [70].

Rhoads and co-workers [70] have identified potential binding sites for the hepatocyte nuclear factor 1 (HNF-1) and major late transcription factor/upstream stimulatory factor (MLTF/USF) in the rat *SGLT1* promoter. Electrophoretic mobility shift assays indicated that HNF-1 β binding exhibited circadian periodicity, suggesting that HNF-1 β regulation contributes to circadian changes in SGLT1 transcription [70]. The HNF-1 and MLTF/USF binding sites are suggestive of the carbohydrate response element found in the liver-type pyruvate kinase [99]. Since carbohydrate concentrations in the rat lumen vary with the time of day [68], these variations may act as a cue to drive or inhibit SGLT1 transcription even if luminal concentrations are out of phase with diurnal changes in SGLT1 mRNA abundance. Forskolin, which increases intracellular cAMP concentrations, has been observed to directly increase intestinal glucose transport [100], but there has been no study on potential second messengers mediating the effect of diet on intestinal glucose transport.

GLUT5

For many years, fructose absorption by the small intestine was thought to have been mediated mainly by a single Na⁺-independent transporter in the brush-border membrane. The fructose transporter was later on found to be a member of the facilitated glucose-transporter family [10]. This transporter is highly stereospecific for fructose, and is not inhibited by phlorizin, which inhibits SGLT1, by phloretin, which inhibits GLUT2, or by cytochalasin B, which apparently inhibits all other GLUTs. GLUT2 has also been widely accepted to be the basolateral sugar transporter, but a recent study has proposed that GLUT2 is also present at the brush-border membrane of normal rat intestine [101], and is therefore available to mediate fructose (and glucose) transport. GLUT2 is thought to be rapidly lost from the brush-

Figure 4 A model of SGLT1 and GLUT5 regulation by diet

Findings from recent studies are compatible with a model proposing that SGLT1 regulation by diet involves perception of the signal and transcription of SGLT1 mainly in crypt cells. As cells migrate to the villus, the mRNA is degraded, and transporter proteins are then synthesized and inserted into the membrane leading to increases in glucose transport after 24 h. In the SGLT1 model, transport activity in villus cells cannot be modulated by diet. The time course of change in glucose transport is due mainly to cell migration. In contrast, GLUT5 regulation by diet involves *de novo* synthesis of GLUT5 mRNA and protein in cells lining the villus, leading to increases in fructose transport 4–8 h after consumption of diets containing fructose. In the GLUT5 model, transport activity can be reprogrammed in mature enterocytes lining the villus column.

border membrane soon after the jejunum is removed from the animal, and hence its presence in the brush-border could not be verified *in vitro*. To complicate matters, GLUT5 has also been found in the basolateral membrane of human enterocytes [102].

Effect of diet

Because the most common sugar in natural fruit juices is fructose, and because high-fructose syrups are used as sweeteners in synthetic juices and carbonated drinks, the average fructose consumption in the United States has increased markedly since the 1980s [103]. Fructose represents about 20% of total daily carbohydrate intake and 9% of total daily caloric intake, but for certain segments of the population, fructose consumption is much higher. Breath hydrogen tests of humans, and particularly of small children, consuming high-fructose-containing drinks indicate some degree of malabsorption in the majority of the test population, indicating that intestinal fructose absorption is limited. However, no mutations were found in the protein-coding region of the *GLUT5* gene in children with clinical evidence of isolated fructose malabsorption (IFM), demonstrating that IFM may not result from the expression of mutant GLUT5 protein [104].

Unlike SGLT1 regulation, the regulation of GLUT5 expression in the small intestine is rapid, and changes in fructose transport are typically paralleled by similar changes in GLUT5 mRNA and protein abundance. In adult rats, the $J_{\max}$ of intestinal fructose transport was initially found to increase 2-fold within three days after consumption of high-fructose diets [105]. This increase in transport activity was later on confirmed to be due to increases in GLUT5 protein and mRNA abundance. GLUT5 protein abundance increases 5-fold just one day after initial consumption of high-fructose pellets by rats, and protein abundance continues to increase gradually as long as fructose

consumption continues [19]. Rat GLUT5 mRNA abundance doubles within 3 h after intestinal perfusion with fructose solutions [106]. Young rats fed on chow but not on casein- or soya-based diets have higher levels of GLUT5 mRNA in the small intestine [38]. Chow would be expected to contain more carbohydrate than soya or casein, but it is not clear how much more fructose there is in the chow-based diet. A fructose-enriched diet does not increase the levels of GLUT5 protein or mRNA in a segment of small intestine that is isolated from the rest of the small intestine, but continues to have mesenteric blood supply. This suggests that regulation requires fructose to interact with the brush border of the small intestine [19].

GLUT5 mRNA abundance and fructose absorption rate in rats increase monotonically with increasing levels of dietary fructose [81], although a content of 30% dietary fructose is required for significant increases in expression. Consumption of pellets containing 65% fructose results in an average intestinal luminal concentration of 26 mM fructose [20]. A pronounced proximal-to-distal gradient in GLUT5 mRNA expression is also suggestive of induction correlated with luminal concentration [107], since concentrations of luminal sugars are typically greater in anterior regions of the small intestine [68]. Regulation of enzymes and transporters involved in sugar metabolism may be linked, because increases in GLUT5 mRNA expression are often accompanied by increases in expression of sucrase isomaltase, SGLT1 and GLUT2 mRNA [43].

Circadian rhythm

Similarly to intestinal glucose transport, fructose transport in adult rats is subject to a strong circadian influence. Compared with GLUT5 mRNA and protein abundance at 09:00 h, mRNA and protein abundance are 2–3-fold greater at 15:00 h, before decreasing towards the early morning hours (end of the dark

cycle) [69,107]. Hence diurnally induced peak expression of GLUT5 coincides with that of SGLT1, and is timed to anticipate increases in food intake. The diurnal changes in GLUT5 expression, unlike those in SGLT1 expression, can be modulated further by changes in dietary substrate levels. A few hours after introduction of dietary fructose in the middle of the dark cycle, GLUT5 mRNA and protein abundance increase approx. 9- and 4-fold respectively above the level expected at the end of the dark cycle before rats were fed with high fructose [69]. Hence the effects of diet and circadian rhythm may be additive.

GLUT5 mRNA is almost non-existent in the crypt, but GLUT5 mRNA abundance is highest in the lower-to-middle villus regions in adult rats. Gavage feeding of fructose solutions for 4 h increases total GLUT5 mRNA abundance, but does not alter the crypt-villus pattern of distribution [108].

Development of transport

During rat development, the expression of GLUT5 is considerably delayed compared with that of SGLT1 (Figure 2). In the rat or the rabbit, SGLT1 is expressed strongly at birth, whereas GLUT5 is expressed in significant quantities only after weaning is completed [16,81,107,109]. There is also strong circumstantial evidence that fructose absorption is delayed in humans. Using breath hydrogen tests that detect small intestinal malabsorption of sugars through the resulting fermentation in the colon, the highest percentage of fructose malabsorption was detected in children aged 1–3 years [110]. Hence small intestinal absorption of fructose is limited, especially in toddlers. The efficiency of absorption seems to increase with advancing age of children [111]. Malabsorption of fructose may be a cause of recurrent abdominal pain and chronic non-specific diarrhoea (toddler's diarrhoea) [112].

Fructose transport rate is modest throughout gestation, and increases significantly during the final 7 days of gestation in rabbits [75]. After birth, this baseline rate of fructose transport decreases gradually in rats and rabbits [16,113]. Later on during development, after the completion of weaning, intestinal fructose transport increases dramatically by 3–6-fold, mimicking the pattern of changes in GLUT5 mRNA abundance [16,81,107,109]. This post-weaning increase in GLUT5 expression is hard-wired and does not need luminal fructose. However, fructose transporter activity and GLUT5 mRNA abundance in rats can be enhanced ahead of this natural schedule by precocious consumption of dietary fructose (Figure 2) [80,81]. This precocious enhancement of GLUT5 expression by its substrate is striking: mRNA abundance increases 3–4-fold, while transport activity increases 2–3-fold. When GLUT5 expression is precociously enhanced, the normally scheduled increase in GLUT5 expression after completion of weaning is no longer observed. Hence ontogenetic regulation of rat GLUT5 expression exhibits both developmental rigidity and flexibility. It is flexible because GLUT5 expression may be enhanced ahead of its natural schedule when dietary fructose is consumed early during the weaning process. It is rigid because GLUT5 expression is enhanced at the completion of weaning, usually aged 28 days or older, whether or not dietary fructose is consumed. It is also rigid because GLUT5 expression can only be enhanced by luminal fructose during the weaning, and not during the suckling stages [114].

GLUT5 activity and mRNA expression in weaning rats are not subject to diurnal rhythms [81], or even to hormonal influences. The precocious enhancement of GLUT5 expression in neonatal rats occurs independently of the well-established

surge in plasma corticosterone [82] and thyroxine [21] concentrations occurring during the transition from suckling to weaning. Rather, precocious enhancement of GLUT5 expression during development is modulated by luminal fructose [115], because GLUT5 expression does not increase in bypassed loops of intestine in rats fed high-fructose pellets. As in adult rats [108], GLUT5 mRNA is absent in the crypt, and is expressed in modest amounts in the lower villus regions. Luminal fructose increases GLUT5 mRNA abundance mainly in enterocytes lining the middle and upper villus regions [114]. Modulation of GLUT5 expression in neonatal rats may involve fructose metabolism, because intestinal perfusion of a non-metabolizable analogue, 3-*O*-methyl fructose, does not increase intestinal fructose transport [114]. This finding, however, is equivocal, because GLUT5 has a lower affinity for 3-*O*-methyl fructose than for fructose.

Mechanisms underlying regulation

In adult rats fed on fructose, increases in transcription rates increase GLUT5 mRNA abundance [43,116]. Except for dietary fructose itself and the disaccharide sucrose, which undergoes hydrolysis to glucose and fructose, other sugars, sugar analogues and metabolites do not alter mRNA abundance and transcription rates of GLUT5 in adult rats [36,43]. Hence, the receptor regulating GLUT5 expression is highly specific. This is in sharp contrast with rat SGLT1, the rate of transcription of which can be stimulated by a variety of sugars.

In adult rats, cycloheximide prevents the dietary fructose-induced increase in both GLUT5 mRNA and protein during the day, but not during the night, indicating that protein synthesis *de novo* is required for regulation of GLUT5 expression during the day [108]. Cycloheximide also prevents the diurnally related increase in GLUT5 mRNA and protein abundance that occurs typically in the afternoon. However, cycloheximide has no effect on evening levels of GLUT5 mRNA and protein.

In contrast with equivocal findings in adult rats, GLUT5 regulation in weaning and suckling rats is quite clear. Injection of actinomycin-D, an inhibitor of mRNA synthesis, before perfusion of the intestinal lumen with fructose completely prevents the fructose-induced increase in GLUT5 mRNA expression and transporter activity, but has no effect on SGLT1 expression and transporter activity [20] (Figure 5). Injection of cycloheximide before intestinal fructose perfusion has no effect on GLUT5 mRNA expression, but prevents the fructose-induced increase in intestinal fructose transport rate. Hence, *de novo* GLUT5 mRNA and protein synthesis is required for the observed increases in fructose transport after fructose feeding (Figure 4). The cycloheximide results also indicate that up-regulation of GLUT5 mRNA abundance does not need *de novo* protein synthesis of transcriptional factors; perhaps increases in intracellular fructose or its metabolites are sufficient to stimulate transcription. Decreased degradation is not a probable mechanism, because GLUT5 mRNA abundance was similar in vehicle-injected and cycloheximide-treated pups perfused with glucose solutions [20].

Dramatic increases in mRNA abundance of immediate-early genes *c-fos* and *c-jun* preceded the increases in GLUT5 mRNA abundance following intestinal fructose perfusion [117]. These transient increases in *c-fos* and *c-jun* mRNA abundance are also prevented by actinomycin D [20], and hence these transcription factors are likely to be involved in the activation of the *GLUT5* gene. However, increases in *c-fos* and *c-jun* mRNA abundance are also observed following intestinal perfusion with glucose, and even mannitol, a non-metabolizable sugar, indicating that these transcription factors respond to a variety of stimuli and become

Figure 5 Effect of transcription and translation inhibitors on GLUT5 induction by diet in neonatal rats

Top panel: Same-age pups were injected with (+act) or without (–act) the transcription inhibitor actinomycin D approx. 12 h before intestinal perfusion with 100 mM fructose or 100 mM glucose in Ringer's solution. Actinomycin D prevented the fructose-induced increases in GLUT5 mRNA and function. Results from unperfused littermates were similar to those from rats perfused with glucose. Glucose and fructose perfusion, as well as actinomycin D, had no effect on SGLT1 mRNA abundance and absorption rate (results not shown). Bottom panel: Same-age pups were injected with (+chx) or without (–chx) the translation inhibitor cycloheximide about 4 h before perfusion with 100 mM fructose or 100 mM glucose in Ringer's solution. Cycloheximide prevented the fructose-induced increases in GLUT5 function only; it had no effect on GLUT5 mRNA abundance. SGLT1 mRNA abundance and glucose uptake were not affected by cycloheximide (results not shown). Modified from Jiang and Ferraris [20], with permission. © (2001) The American Physiological Society.

involved in the activation of other genes. In fact, perfusion-induced increases in *c-fos* and *c-jun* mRNA abundance occur in all enterocytes along the villus, whereas those of GLUT5 occur mainly in enterocytes along the upper villus and villus tip regions [114,117].

The human *GLUT5* promoter region contains cAMP response elements [23]. Treatment of differentiated Caco-2 cells with the adenylate cyclase stimulator forskolin dramatically increases fructose uptake, GLUT5 protein abundance and GLUT5 mRNA, suggesting that cAMP plays an important role in GLUT5 regulation. cAMP increases both the GLUT5 transcription rate and the stability of GLUT5 mRNA. These important observations using Caco-2 cells await confirmation by studies utilizing the small intestine. Protein kinase C (PKC) has also been recently implicated in the regulation of rat intestinal fructose transport [118], except that PKC reportedly increases fructose transport not by increasing GLUT5 activity, but by recruiting GLUT2 to the brush-border membrane. Since GLUT2 transports both fructose and glucose, the recruitment of GLUT2 to the brush-border membrane will also enhance fructose transport. No other laboratory has made this interesting observation in the past because GLUT2 is supposed to be lost from the brush-border within minutes *in vitro* [119].

FUTURE STUDIES

I propose the following topics for future work. (1) Distinguishing acute from chronic dietary regulation, and regulation by diet from regulation by circadian factors. GLUT5 seems to respond rapidly to changes in dietary or luminal fructose concentration, and this response is independent of diurnal changes in GLUT5 expression. SGLT1 regulation is complicated because it has two or three time scales: a diurnal rhythm, which may be coupled with a short-term response to feeding, and a longer-term response to diet that seems to be tightly linked to enterocyte migration.

(2) The signal and mechanism underlying regulation of intestinal SGLT1 expression by dietary Na^+ . Although recent work has been remarkably consistent among many laboratories, intestinal luminal concentrations of Na^+ are already high (≈ 125 mM) in rabbits and dogs [68], and remain high regardless of time of day, intestinal region, diet and feeding status. Consumption of high-salt diets is unlikely to change luminal Na^+ concentrations because of the high paracellular permeability of the small intestine. If steady-state luminal Na^+ concentrations do not change significantly with consumption of a high-salt diet, what then causes the increase in glucose transport? Can this dietary Na^+ -dependent increase be demonstrated in other Na^+ -dependent transport systems?

(3) The identification and role of neuroendocrine components in diurnal regulation, and the role of luminal nutrients and factors. Although the evidence for neuroendocrine factors is strong, the fact that circadian rhythmicity was observed for monosaccharide transport in rats fed orally, but was not observed in rats fed intravenously [67], suggests a role for luminal factors, even if the circadian rhythm of changes in luminal nutrient concentrations is out of phase with changes in transporter gene expression.

(4) The identification of signalling pathways for SGLT1 and GLUT5 regulation in the small intestine. SGLT1 is known to contain consensus sites for phosphorylation by protein kinases [5,120] and the *GLUT5* promoter contains two cAMP-response elements [23]. The signalling pathway could differ among the different types of regulation (diurnal, short-term and long-term dietary).

(5) Modulation of GLUT5 by its substrate in neonates. Why is it possible to enhance fructose transport in weaning, but not in suckling, rats? Why is GLUT5, but not SGLT1, expression suppressed during early development? What is the nature of hard-wired developmental cues that turn on GLUT5 in post-weaning rats independently of luminal substrate signals?

(6) The recent proposal by Kellett [7] that apical GLUT2 transporters play an important role in intestinal glucose and fructose absorption. Corpe and co-workers [121] have very recently demonstrated that GLUT5 trafficks to the brush-border membrane, whereas GLUT2 trafficks to the basolateral membrane of rat intestine. It will be interesting to test this proposal in animals whose diets include very concentrated sugar solutions, such as nectarivorous birds for which the passive pathway [122] of glucose absorption has been proposed [123,124].

(7) Expression of SGLT1 and GLUT5 in other animals may yield information relevant to our understanding of regulation of sugar transport. Rodents typically regulate sugar transport over a range of approx. 2–3-fold, whereas birds do not [50]; in contrast, sheep [85] and pythons [125] regulate transport ≈ 50 –100-fold. What are the molecular bases for these marked species-related differences in magnitude of regulation?

(8) Crypt-villus site of dietary enhancement of SGLT1 and GLUT5 transcription rate or mRNA abundance. Although there has been a number of studies showing the steady-state

levels of SGLT1 message along the crypt–villus axis, there need to be studies showing the effects of dietary carbohydrate on the crypt–villus site of SGLT1 or GLUT5 transcription.

(9) Quantitative partitioning of contributions by various adaptive mechanisms to changes in absorptive capacity, and quantitative comparisons between absorptive capacity and dietary intake [3]. Although I have proposed mostly studies that increase our understanding of cellular mechanisms underlying regulation of intestinal sugar transport, the quantitative aspects that relate these adaptations to the whole animal may be a key to understanding why regulation occurs at all.

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