# Intestinal Transport of Monosaccharides

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**Summary**

Sugars are transported from the small intestinal lumen to blood circulation by transcellular or paracellular routes. The transcellular process needs protein transporters to mediate monosaccharide to cross lipid cell membranes. The facilitated-diffusion glucose transporter 5 (GLUT 5) facilitates fructose entering the enterocytes. $Na^+$-dependent glucose transporter 1 (SGLT 1) actively transport glucose and galactose across the epithelial cell layers by sodium gradient within the enterocytes. This mechanism is maintained by the $Na^+$-$K^+$ ATPase enzyme located at basolateral membrane (BLM). All sugars exit from the enterocyte to blood circulation by facilitation of GLUT 2 at BLM. Regulation of the paracellular transport of glucose involves the tight junction permeability.
**Keywords**: Sugar; Small intestine; Absorption; SGLT1; GLUT

## Introduction

Carbohydrates are the most abundant of the four major biomoleculars which include proteins, nucleic acids, and lipids. The primary carbohydrates in the human diet are starches, sugars, and dietary fibers (Table 1). Sugars and starch are digested to monosaccharides, mostly glucose, galactose, and fructose, prior to their absorption across the epithelial cells of the small intestine. Once absorbed, galactose, and fructose are mostly converted to glucose for metabolism or storage in the body (Wright et al., 2003).

**Table 1**. Class of carbohydrate

| Class | Type | Constitution |
|---|---|---|
| Polysaccharides | starch | glucose |
| | glycogen | glucose |
| | galactomannan | galactose, mannose |
| | β-glucan | glucose |
| Disaccharides | sucrose | glucose-fructose |
| | lactose | glucose-galactose |
| | maltose | glucose-glucose |
| Monosaccharides | glucose, fructose, galactose | |

The regulation of intestinal sugar absorption is limited at the step across the brush border membrane (BBM) and the basolateral membrane (BLM) of epithelial cells. Changes in absorption rates can be accomplished by specific or nonspecific mechanisms. Specific mechanisms, such as changes in affinity for a substrate or changes in number of sugar transporters, are those that increase the absorption rate of a nutrient or category of nutrients sharing a single transport system. Nonspecific mechanisms, such as increase in the length and numbers of intestinal villi, are induced during pregnancy, lactation, or following intestinal resection (Karasov & Diamond, 1983).

An increase in the amount of dietary carbohydrates appeared to enhance rates of glucose absorption (Ferraris & Diamond, 1986). The increase in absorptive rate is related to the activity of sugar-transporters at BBM and BLM, which is reversible

and under specific regulation. For example, when a mouse was switched from a non-carbohydrate to a high-carbohydrate diet, the numbers of glucose transporters were double within less than a day, and the number reverted to the beginning level when the mouse was switched back to a non-carbohydrate diet (Diamond, 1991). The objective of this article is to review the specific mechanism of sugar transport across the epithelial cell membrane of the small intestine to blood circulation in healthy individuals.

**Mechanism of sugar absorption**

Enterocytes in the small intestine are joined by tight junction, which maintains the polarity of the enterocyte with apical BBM and BLM (Woudstra & Thomson, 2002). Monosaccharides are absorbed by the mature enterocytes on the upper third of the villi in the jejunum and ileum (Wright et al., 2003). Sugars are absorbed by the transcellular or paracellular routes (Figure 1).

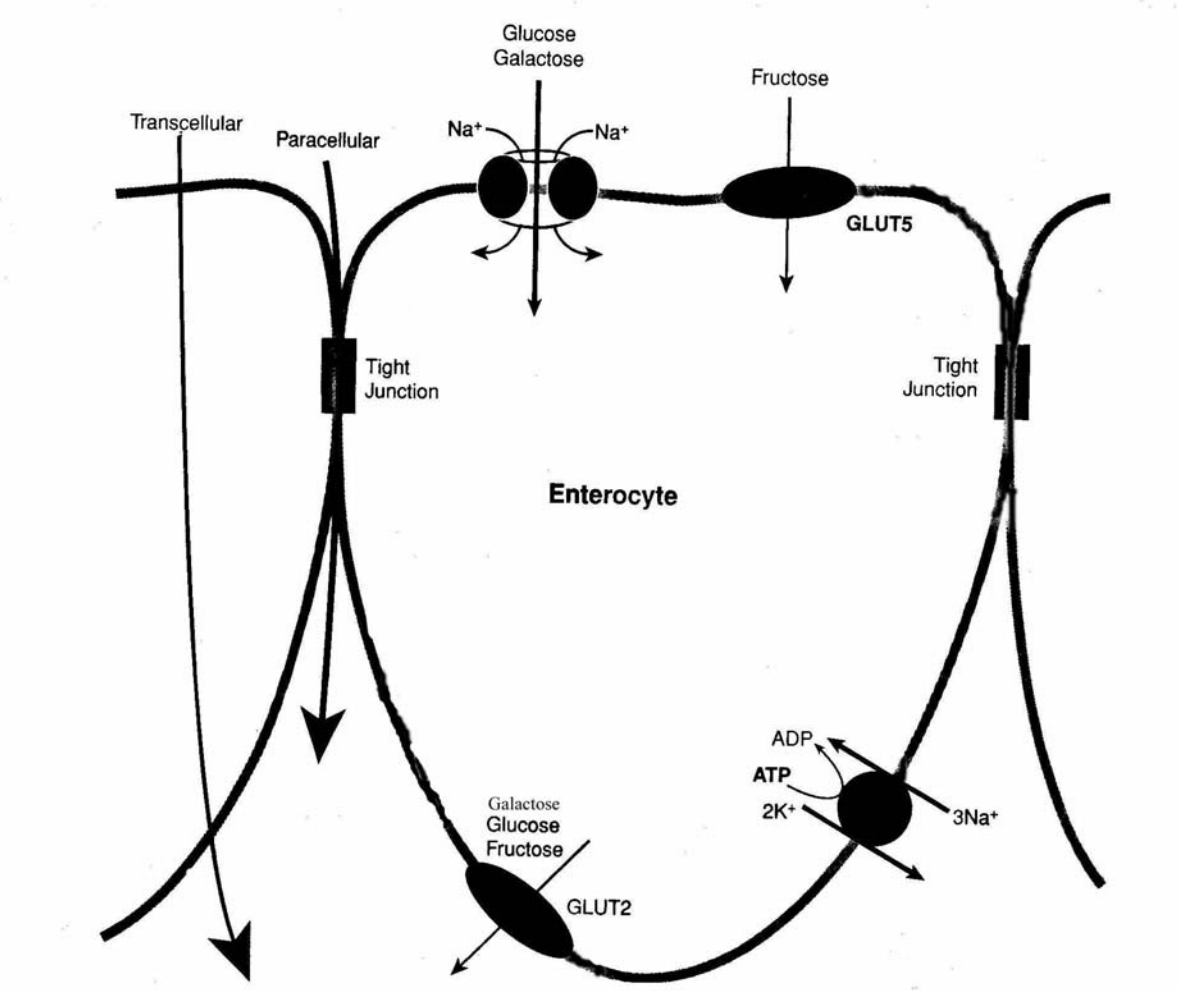


**Figure 1**. Classical model of sugar absorption. $Na^+$-dependent glucose transporter actively transports glucose and galactose across the BBM. Fructose is transported across the BBM by facilitative GLUT 5. GLUT2 transports glucose, galactose, fructose across the BLM via facilitative diffusion (from Traber, 2004).

**Transcellular route**

Sugars are hydrophilic molecules that are unable to cross lipid cell membranes in the absence of protein-transporters. There are two families of glucose transporters: sodium-dependent glucose transporter (SGLT) family and facilitated-diffusion glucose transporter (GLUT) family as shown in Table 2. These proteins mediate sugar transport with different efficiencies and kinetics. In the small intestine, SGLT1, GLUT2, and GLUT5 serve in the absorption of monosaccharides hydrolyzed from dietary carbohydrates.

**Table 2**. The family of glucose transporters

| | Major site of expression |
|---|---|
| $Na^+$-dependent glucose transporter (SGLT) | |
| SGLT 1 | small intestine, kidney |
| SGLT 2 | kidney |
| Facilitated-diffusion glucose transporter (GLUT) | |
| GLUT 1 | brain, erythrocytes, placenta, fetal tissue |
| GLUT 2 | small intestine, liver, kidney, pancreatic β-cell |
| GLUT 3 | brain |
| GLUT 4 | skeletal muscle, adipose tissue |
| GLUT 5 | small intestine |
| GLUT 6 | psuedogene which is not expressed at the protein level |
| GLUT 7 | intestine, colon, testis (the physiological relevance is being investigated) |
| GLUT 8 | testis |
| GLUT 9 | kidney, liver |
| GLUT 10 | heart, lung, brain, liver |
| GLUT 11 | liver, brain, lung |
| GLUT 12 | heart, muscle, brown adipose tissue |

*Note*. Modified from Uldry & Thorens, (2004) and Wright et al, (2007).

Glucose and galactose are transferred across the BBM of the enterocytes by the action of SGLT 1. When the glucose concentration in the intestinal lumen is lower than that in the plasma (maintained at 5 mmol/L), SGLT 1 transports the glucose uphill against its concentration gradient. This transcellular pathway is powered by a downhill gradient of $Na^+$ across the apical membrane, which is maintained by the basolateral $Na^+/K^+$-ATPase (Kellett & Brot-Laroche, 2005) (Figure 1).

Fructose is passively transported across BBM by a specific facilitative glucose transporter 5 (GLUT 5). All three sugars are transported out of the enterocyte across the BLM by a passive process (Figure 1). The $Na^+$-independent facilitative glucose transporter 2 (GLUT 2) is exclusively expressed in the BLM of intestinal absorptive cells. GLUT 2 is capable of transferring glucose, fructose, and galactose from absorptive cells to the blood stream (Thorens et al., 1990).

SGLT 1

SGLT 1 is expressed in the BBM of the small intestine. It consists of 14 transmembrane α-helices, with both the N-and C-terminal residues facing the extracellular side of the plasma membrane (Figure 2). The transporter contains phosphorylation sites between transmembrane helices 6 and 7, and between transmembrane helices 8 and 9 (Wright et al., 1992). The phosphorylation sites involve the sugar transport which will be discussed below.

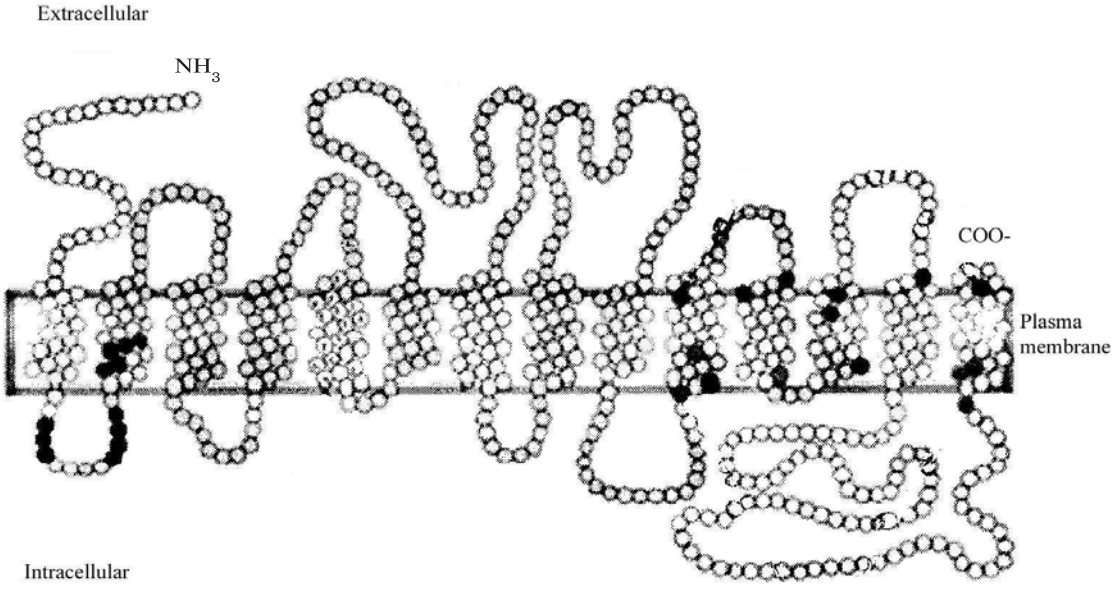


**Figure 2**. The structure of SGLT 1. SGLT1 consists of 14 transmembrane α-helices, with both the N-and C-terminal residues facing the extracellular side of the plasma membrane (modified from Wright et al., 2007).

Each glucose molecule is transported together with two sodium ions binding to SGLT 1, down its electrochemical potential gradient across the BBM (Turk et al., 1996). Since intracellular concentration of $Na^+$ in cytosolic site is low (10 vs. 140 mEq/L) and the affinity of $Na^+$ inside enterocyte is also low, the glucose and galactose enter the cell by the $Na^+$ dissociate (Wright et al., 2003). Sodium can be replaced by $H^+$ or $Li^+$, but the affinity for glucose decreases. The apparent Michaelis affinity constant (Km) of $H^+$ or $Li^+$ is higher than that of $Na^+$.

The $Na^+$-$K^+$-ATPase in the BLM is responsible for maintaining the $Na^+$ and $K^+$ electrochemical gradient across the cell membrane. The $Na^+$-$K^+$-ATPase contains a 110 kDa $\alpha_1$ catalytic subunit, and a highly glycosylated 55 kDa $\beta_1$ subunit (Fambrough et al., 1994). It was shown that the continuously maintained outward $Na^+$ gradient accomplished by the $Na^+$-$K^+$-ATPase on the BLM was the primary asymmetry providing the driving force for active sugar transport. The phenomenon was considered to be secondary active transport, as the hydrolysis of ATP was indirectly coupled to glucose transport via this electrochemical gradient (Crane, 1965).

SGLT 1 contains a number of potential protein kinase A (PKA) and protein kinase C (PKC) phosphorylation sites (Kennelly & Krebs, 1991). It was reported that PKA activation increased glucose transport by 30%, while PKC activation reduced the transport by 60% (Wright et al., 1997). Using a model of activation of PKA and PKC in oocytes, Wright et al (1997) reported that alterations in the number of transporters in the plasma membrane and the changes in the surface area of the membrane contributed to the change in maximal transport rates (Vmax). Since endocytosis and exocytosis alter the membrane surface area, the findings of the effects of PKA and PKC on SGLT 1 suggest that these proteins may be involved in the regulation of glucose transport. However, they also found that the effects of PKA and PKC critically depended on the sequence of the co-transporter being expressed in the oocytes. For example, PKC inhibited rabbit and rat SGLT 1 but stimulated human SGLT 1.

This indicates that the regulation by these kinases may be indirect, since the effect of PKC was independent of the presence or absence of phosphorylation sites on SGLT 1 (Wright et al., 1997).

D-glucose stimulates the synthesis of rat and human SGLT 1 in the small intestinal cells. The glucose sensor in the lumen transduces a signal through a cascade of intracellular events, leading to the transcription of the SGLT 1 gene, translation of SGLT 1 mRNA, and the insertion of functional SGLT 1 protein into the BBM of the enterocyte (Dyer et al., 1994; Shirazi-Beechey, 1995). It was found that intestinal infusion of D-glucose induced rat SGLT 1 expression in the BBM of enterocytes at below the crypt-villus junction, and the SGLT 1 expression was spreading to the villus tip. In contrast, the decrease of sugars in the lumen reduces over 50-fold in the levels of SGLT 1 protein and mRNA (Vayro et al., 2001).

Other sugars are bound to and transported by SGLT 1 but with lower affinity than that for glucose. The affinity to SGLT 1 of other sugars relative to D-glucose in order of decreasing affinity is as the following: D-glucose > α-methyl-D-glucose > D-galactose > 3-O-methyl glucose > L-glucose and 2-deoxyglucose (Ikeda et al., 1989).

Facilitated-diffusion glucose transporters (GLUT)

The member of GLUT family has the sequence structure of 12 transmembrane domains with intracellular N- and C- terminals (Figure 3). Each member of the GLUT family is different in functional characteristics e.g. their substrate specificity, their Km values, and their binding-affinities to the inhibitory ligands e.g. cytochalasin B and forskolin (Joost & Thorens, 2001). GLUT 2 and GLUT 5 will be discussed in this article because they are responsible for the absorption of sugars across the enterocytes of the small intestine.

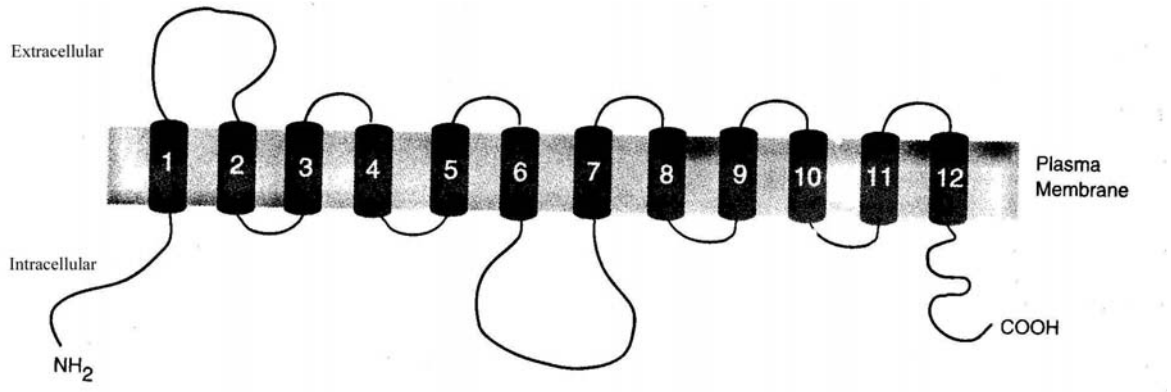


**Figure 3**. Structure of the GLUT family. The monomer has the sequences structure of 12 transmembrane domains with intracellular N and C terminals (from Elsas & Longo, 1992).

GLUT 5

GLUT 5 is a fructose-facilitative transporter, which is expressed at the BBM in the small intestine (Rand et al., 1993). GLUT 5 is a 43-kDa protein with 12 transmembrane domains. GLUT 5-mRNA is found in the lower and midvillus regions of the intestine, with little expression in the villus tips and no detectable expression in the crypts. GLUT 5 mRNA levels in rats were higher in the proximal small intestine when compared to the distal small intestine. It was also found that human GLUT 5 mRNA levels increased with age and were highest in the adult small intestine (Davidson et al., 1992).

The response of GLUT 5 to dietary sugars had been investigated. High fructose diet (50%, w/w) significantly increased the maximum velocity (Vmax) of fructose across

the BBM in rats, and also up-regulated GLUT 5 protein and mRNA abundance, leading to a 2-fold increase of the maximum uptake of intestinal fructose transport (Crouzoulon & Korieh, 1991). A study of feeding sugar-enriched diets (55% D-glucose, D-galactose, D-fructose, D-mannose, D-xylose or 3-O-methylglucose) to male Sprague Dawley rats for 5 days showed that the GLUT 5 mRNA abundance and its transcription rates were increased only by dietary D-fructose, but not by other sugars, sugar analogues and metabolites (Miyamoto et al., 1993). Contrary, Olson and Pessin (1996) reported that high fructose diet did not increase GLUT 5 mRNA. They suggested that there may be an alternative transport pathway for monosaccharide generated from sucrose. However, this suggestion requires further investigation.

GLUT 2

GLUT 2 is a high-capacity, low-affinity facilitative transporter, which is expressed in the intestinal mucosa, hepatocytes, pancreatic cells, and kidney (Fukumoto et al., 1988; Thorens et al., 1988 &1992). It has 12 transmembrane domains, with intracellular N- and C- terminals (Figure 3). In the epithelial cells, GLUT 2 is expressed exclusively in the BLM. It is responsible for the exit of glucose, galactose, and fructose from the cytosol of enterocytes to the blood circulation (Thorens, 1992 & 1993). The rate-limiting step for sugar absorption across the enterocyte is its exit across the BLM. It has been reported that increasing the carbohydrate content of the diet increases the glucose transport capacity at the BLM (Cheesman & Harley, 1991).

GLUT 2 expression increases as enterocytes migrate up from the crypt to the villous tip. GLUT 2 mRNA transcripts were detected in the lower and midvillus regions of the intestine, with minimal expression detected in the villus tips or crypts (Burant et al., 1994). GLUT 2 mRNA was increased by D-glucose, D-galactose, and D-fructose, but not by 3-O-methylglucose, D-mannose, or D-xylose (Miyamoto et al., 1993).

Luminal sugars stimulate GLUT 2 expression and activity. The study of feeding sugar-enriched diets to male Sprague-Dawley rats for 5 days showed that GLUT 2 mRNA was up-regulated by fructose, glucose and galactose. It was unaffected by 3-O-methylglucose, a non-metabolized glucose analog. This indicates that GLUT 2 modulation required intracellular metabolism of the sugar (Miyamoto et al., 1993).

GLUT 2 in the BBM

GLUT 2 was first found in the BLM of diabetic rats (Corpe et al., 1996). The study showed that fructose absorption in diabetic rats was increased by 60%. Since the only transporters known to transport fructose were GLUT 5 and GLUT 2, they revealed that not only GLUT 5, but also large amount of GLUT 2 were present at the BBM of diabetic rats. In contrast, normal rats in control groups did not show significant BBM-GLUT 2. Thus targeting of BBM-GLUT 2 appeared to reflect the pathology of diabetes. GLUT 2 transports both fructose and glucose; therefore, the recruitment of GLUT2 to the BBM will also enhance fructose transport (Kellett & Helliwell, 2000).

Luminal glucose promotes the rapid insertion of GLUT 2 into the BBM. Using a model of BBM SGLT 1, Kellett & Helliwell (2000) proposed that after a meal is ingested, luminal glucose concentrations increase. Glucose uptaken via SGLT 1 may trigger the entry of $Ca^{2+}$, activating PKC-βII and promoting the insertion of GLUT 2 in the BBM.

**Paracellular route**

In addition to the transcellular route of absorption, sugars may pass from the intestinal lumen to the circulation via the paracellular route. This route involved the tight

junction which is the site between enterocytes. The concept of paracellular route had occurred when there were evidences to show that the glucose transport increased linearly to several hundred millimolar although SGLT 1 was already saturated at 30-50 mM glucose (Lostao et al., 1991). These findings suggest that there is possibly a passive component that does not appear to be saturable. It has been hypothesized that the activation of the glucose transporter at the BBM stimulates condensation of the perijunctional ring actomyosin associated with the tight junction, resulting in its contraction. Due to this contraction, the tight junction is opened; therefore, the permeability between enterocytes increases (Madara & Pappenheimer, 1987).

The study of 10-25 mM glucose perfused into isolated segments of hamster small intestine showed that there were large dilatations within junctions following glucose perfusion (Pappenheimer & Reiss, 1987). Researchers concluded that the $Na^+$-coupled transport of solutes from the lumen to the cytosol provides the driving osmotic force for the absorption of fluid and nutrients, and triggers the widening of intercellular junction, thus promoting the bulk absorption of nutrients by solvent drag. At high glucose concentrations, passive component contributes 3-5 times as much as the active component (Lostao et al., 1991). Atisook and colleagues (1990) also proposed that the paracellular transport accounted for 30% of absorbed glucose when luminal glucose concentrations were relatively high.

## Conclusions

SGLT 1, GLUT 2, and GLUT 5 are the regulators that transport monosaccharides across the intestinal epithelium to the blood circulation. The mechanism of GLUT 2 in the BBM is being intensively investigated. There is still much to be studied about the substrate specificity and the kinetics. Future research will expand the knowledge in gene regulations and the function. This will contribute to the understanding of the regulation of intestinal gene expression.

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