Major Glucose Transporters in the Intestinal Epithelium and Their Mechanisms of Action: Postprint

Authors: Lu Yao, Sun Peipei, Song Military

Date: 2018-12-20T00:00:00+00:00

Abstract

Intestinal glucose absorption is primarily mediated by Na+-dependent glucose transporter 1 (SGLT1) and facilitative glucose transporter 2 (GLUT2). Many factors influencing intestinal glucose absorption function achieve their effects by regulating the transcriptional levels, mRNA stability, and protein levels of SGLT1 and GLUT2. Research on the structure and function of glucose transporters not only provides potential drug targets for human diseases such as obesity and diabetes but also offers insights for modulating nutrient absorption in animals. This review summarizes the functions of the major intestinal epithelial glucose transporters SGLT1 and GLUT2 and the factors affecting their expression in the intestinal epithelium, aiming to elucidate intestinal glucose absorption and the regulation of systemic glucose homeostasis at the molecular level.

Full Text

Major Glucose Transporters in Intestinal Epithelium and Their Mechanisms of Action

LU Yao, SUN Peipei, SONG Daijun*
(College of Animal Science and Technology, Southwest University, Beibei 400715, China)

Abstract

Glucose absorption in the intestine is primarily mediated by sodium-dependent glucose transporter 1 (SGLT1) and facilitative glucose transporter 2 (GLUT2). Numerous factors influencing intestinal glucose absorption function exert their effects by regulating SGLT1 and GLUT2 at the transcriptional level, mRNA

stability, and protein level. Studies on the structure and function of these glucose transporters not only provide potential drug targets for human diseases such as obesity and diabetes but also offer insights for modulating nutrient absorption in animals. This review summarizes the functions of the major intestinal glucose transporters SGLT1 and GLUT2 and the factors affecting their expression in intestinal epithelium, aiming to elucidate glucose absorption in the intestine and the regulation of systemic glucose homeostasis at the molecular level.

Keywords: glucose; transporter; intestinal epithelium; SGLT1; GLUT2; mechanism

---

Monosaccharide absorption across the intestinal epithelium relies primarily on transporter-mediated transmembrane transport. Three major families of monosaccharide transporters have been identified: sodium-dependent glucose transporters (SGLTs), facilitative glucose transporters (GLUTs), and the recently characterized sugars will eventually be exported transporters (SWEETs) found in plants and bacteria [1-2]. SGLTs mediate monosaccharide transport dependent on Na+ concentration gradients, co-transporting glucose and galactose. Six subtypes have been discovered, with SGLT1 being the primary mediator of glucose and galactose transmembrane transport in the intestine. GLUTs belong to the major facilitator superfamily (MFS) and are proteins containing approximately 500 amino acids. Fourteen GLUT members have been identified and divided into three subgroups based on amino acid sequence similarity [3]: Class I includes GLUT1-4 and GLUT14; Class II includes GLUT5, 7, 9, and 11; and Class III includes GLUT6, 8, 10, 12, and 13 (HMIT). Among these, GLUT5 is primarily located in the apical membrane of small intestinal epithelial cells, mediating fructose transport, while GLUT2 resides in the basolateral membrane, exporting monosaccharides such as glucose, fructose, and galactose. Research on SWEETs has focused mainly on bacteria and plants, with limited studies on the structure and function of mammalian small intestinal epithelial SWEET transporters, which may primarily transport monosaccharides.

Glucose serves as the primary energy source for life activities, and its digestion and absorption in the intestine is critical for utilization. Glucose transport across intestinal epithelium depends mainly on SGLT1. However, after feeding, when intestinal luminal glucose concentration rises sharply and SGLT1 reaches its maximal transport velocity, the high-capacity GLUT2 is rapidly recruited to the apical membrane of intestinal epithelial cells to participate in glucose absorption. Recent studies indicate that GLUT2 recruitment to the apical membrane is regulated by protein kinase CβII (PKCβII). Through this adaptive mechanism, the body maximizes glucose absorption. High-concentration glucose absorption via SGLT1 and GLUT2 also serves as a signaling pathway to regulate gastrointestinal hormone release. Glucose transport is a rate-limiting step in its utilization and a highly regulated process, with many factors affecting glucose absorption acting through modulation of glucose transporter gene transcription,

mRNA stability, and protein levels. This review examines the mechanisms of glucose absorption in intestinal epithelium from the perspectives of SGLT1 and GLUT2 structure, function, and factors influencing their expression.

1.1 SGLT1

SGLT1, also known as sodium-glucose transporter 1 or Na+/glucose cotransporter 1, is encoded by the human SLC5A1 gene and belongs to the APC (amino acid polyamine) superfamily [4], exhibiting high homology across species. Structurally, SGLT1 contains 14 transmembrane helices (TMs) and features a core "LeuT" fold characteristic of the APC superfamily, composed of a pair of "5+5" inverted repeat sequences formed by TM2-6 and TM7-11. These TM bundles collectively form the active center of SGLT1, which contains numerous conserved residues that bind glucose molecules through hydrogen bonds [5]. These structural features underlie SGLT1 transport function, which depends on conformational changes between outward-facing and inward-facing structures to achieve Na+ and glucose cotransport [6]. SGLT1 is highly expressed in villus epithelial cells of adult animal small intestine and also in crypt cells [7]. Expression levels in the small intestine follow the pattern: jejunum > duodenum > ileum, with no SGLT1 expression in large intestinal epithelium. SGLT1' s primary substrates are glucose and galactose [Michaelis constant (Km) 0.5 mmol/L], transported across the membrane with stoichiometric ratios of 2 Na+:1 glucose and 1 Na+:1 galactose. Substrates transported by SGLT1 must be pyranose sugars in ring form; reducing the number of hydroxyl groups on monosaccharides by 1-6 decreases apparent affinity for SGLT1 by 5-200 fold, and substitution of certain hydroxyl groups on the sugar ring significantly reduces affinity. In addition to glucose and galactose, SGLT1 can transport β-hydrophobic glycosides such as phenyl-β-D-glucose [4]. Furthermore, SGLT1 exhibits water transport capacity between 4.5$×10^{-16}$ and 2.7$×10^{-13}$ cm^3/s, 1-3 orders of magnitude lower than aquaporins, but due to high SGLT1 expression in intestinal epithelium, it may serve as a major pathway for water absorption [8]. Phlorizin, a flavonoid, is a classic competitive inhibitor of SGLT1 and has been used in functional studies and for prevention and treatment of type 2 diabetes.

1.2 GLUT2

GLUT2, also known as facilitative monosaccharide transporter 2 or Na+-independent monosaccharide transporter 2, is encoded by the human SLC2A2 gene and belongs to the major facilitator superfamily (MFS). Structurally, GLUT2 contains 12 transmembrane α-helices, with N-terminal TM1-6 and C-terminal TM7-12 forming a pair of inverted repeat structures—the MFS fold. Amino acid residues in the GLUT2 active center bind glucose molecules via hydrogen bonds and complete monosaccharide transport through conformational changes [9]. GLUT2 was first identified from mouse and human liver cDNA libraries. It is widely distributed in various tissues including liver, small intestine, kidney, pancreatic β-cells, as well as in neurons, astrocytes, and

ependymal cells, where it performs diverse functions [10]. In the intestine, GLUT2 primarily functions in the basolateral membrane of epithelial cells, exporting intracellular monosaccharides into the bloodstream, but can also be recruited to the apical membrane to participate in glucose absorption under high luminal glucose conditions. Compared to other glucose transporters, GLUT2 has low apparent affinity for glucose (Km 17 mmol/L) and can also transport galactose (Km 92 mmol/L), mannose (Km 125 mmol/L), and fructose (Km 76 mmol/L), but exhibits high affinity for glucosamine (Km 0.8 mol/L) [3]. Corpe et al. [11] reported that GLUT2 can also transport vitamin C and its oxidized form dehydroascorbic acid (Km 2.33 mmol/L). Cytochalasin b and phloretin are potent inhibitors of GLUT2.

2.1 SGLT1

Glucose and galactose absorption in small intestinal epithelium primarily depends on SGLT1, which drives substrate molecules to cotransport with Na+ using the electrochemical gradient established by high extracellular Na+ concentration. The balance between membrane electrochemical gradients and intracellular osmotic pressure is maintained primarily by Na+,K+-ATPase [12]. First, the specific glucose binding site is located in a structural center formed by a set of inverted repeat TMs (TM2-6 and TM7-11) near the center of the phospholipid bilayer, surrounded by two Na+ binding sites with different affinities. These TM bundles contain many conserved amino acid residues, mostly polar or aromatic. Polar residues bind hydroxyl groups on the sugar ring through hydrogen bonds, while aromatic residues stack with the pyranose ring; mutations in these residues cause severe glucose and galactose malabsorption. Second, other conserved hydrophobic amino acids form closed "gates" at both ends of the TMs, surrounding the monosaccharide molecule in a "sandwich" structure. During transport, SGLT1 first forms an outward-facing conformation; Na+ enters from the extracellular side and binds to its binding sites, promoting rearrangement of the TM bundles to expose the substrate binding site and increase affinity for glucose molecules. Glucose binding further induces TM rearrangement to close the extracellular gate. Subsequently, conformational changes in the intracellular segments of the TMs open the intracellular gate to form an inward-facing conformation, releasing sugar molecules and Na+ into the cell. Finally, SGLT1 returns to its pre-transport conformation, re-exposing its specific binding site to complete the next transport cycle [5].

After feeding, to maintain stable blood glucose concentration, digestive tract secretory cells secrete gastrointestinal hormones that promote insulin secretion, with gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) being the most potent. The release of GIP and GLP-1 in intestinal epithelium is closely related to SGLT1 and GLUT2 function. Röder et al. [13] reported that GIP and GLP-1 concentrations were reduced by nearly 6- and 10-fold, respectively, in SGLT1-deficient mice. After feeding, increased luminal glucose concentration induces GLUT2 recruitment to the apical membrane to participate in

glucose absorption together with SGLT1. On one hand, SGLT1 cotransports glucose molecules and Na+, depolarizing intestinal L-cells, opening voltage-gated Ca2+ channels, triggering Ca2+ influx and intracellular Ca2+ release from stores, and stimulating GLP-1 release via exocytosis (Figure 1 [Figure 1: see original paper]). On the other hand, ATP generated from glucose metabolism within cells closes ATP-sensitive K+ channels, increasing the membrane potential difference and enhancing GLP-1 release [14]. Taste receptors T1R2+T1R3 can bind luminal glucose or glucose analogs, activating α-gustducin to participate in GIP and GLP-1 release through downstream signaling pathways [15]. Indeed, the secretion of many insulinotropic gastrointestinal hormones such as cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide-2 (GLP-2), and neurotensin from enteroendocrine cells depends on these mechanisms [16-17]. In summary, SGLT1 and GLUT2 function not only as monosaccharide transporters but also as sensors of luminal glucose concentration changes, inducing release of glucose metabolism hormones to maintain normal blood glucose concentration. Consequently, SGLT1 has become a therapeutic target for type 2 diabetes.

Figure 1 caption: The functions of SGLT1 and GLUT2 in intestinal epithelia [14]

2.2 GLUT2

The *E. coli* D-xylose transporter XylE shares 20%-29% homology with human GLUTs, and its crystal structure serves as a model protein for studying the MFS superfamily. GLUT2' s transport mechanism is similar to XylE' s, where extracellular solutes enter the transport center through a narrow channel and bind to polar amino acids via hydrogen bonds. Any missense mutation in these residues completely abolishes transport activity. Subsequently, GLUT2 undergoes conformational changes that alternately expose the substrate binding site to both sides of the membrane, completing substrate transport. This series of conformational changes depends on TM rearrangement, positional shifts, and formation and breakage of salt bridges within TM bundles [18]. Unlike SGLT1' s active glucose transport, GLUT2 transports glucose along its concentration gradient in an energy-independent manner.

In the classical model of glucose absorption, GLUT2 was thought to be expressed only in the basolateral membrane of intestinal epithelial cells, primarily exporting monosaccharides from epithelial cells into the circulatory system. Whether GLUT2 can be recruited to the apical membrane to participate in glucose and fructose absorption has been controversial, with many in vitro studies failing to detect GLUT2 in the apical membrane or finding very low density, possibly due to differences in detection methods. Apical GLUT2 can be detected by four different antibodies targeting its C-terminus, N-terminus, and intra- and extracellular loop epitopes, but immunohistochemical methods using C-terminal antibodies cannot detect apical GLUT2 [19]. After feeding, the sharp increase in luminal glucose concentration can induce transient insertion of GLUT2 into

the apical membrane of intestinal epithelial cells. Due to GLUT2' s high transport capacity and non-saturable characteristics, it can cooperate with SGLT1 to accelerate glucose absorption [20]. GLUT2 recruitment to the apical membrane has important physiological significance: it adapts to high luminal glucose concentrations to enhance absorption, and for intestinal epithelial cells themselves, GLUT2' s Na+-independent passive glucose transport does not impose the ionic and osmotic burden associated with SGLT1-mediated transport.

3 Factors Affecting Glucose Transporter Expression

3.1 Substrate Levels Luminal glucose concentration changes dramatically before and after feeding. After feeding, dietary carbohydrates are extensively digested to produce glucose, significantly increasing luminal glucose concentration. Correspondingly, SGLT1 and GLUT2 expression in the apical membrane of intestinal epithelial cells increases markedly to enhance glucose absorption [21]. Luminal glucose molecules are key regulators of SGLT1 and GLUT2 expression. Glucose binds to intestinal epithelial cell taste receptors T1R2+T1R3, activating the coupled G protein (α-gustducin) and downstream signaling pathways. On one hand, this activates phospholipase C$ 2(PLC 2)$orproteinkinase A($PKA$); PLC 2generatesthesecondmessengerdiacylglycerol, whichtogetherwi activatesPKC\ II, akeyfactorinGLUT2recruitmenttotheapicalmembrane$[22].$PKC$ \$II regulates GLUT2 translocation from intracellular reserve pools to the apical membrane via exocytosis through phosphorylation activation and ubiquitination degradation, adapting to luminal glucose concentration [23]. On the other hand, T1R2+T1R3 activation triggers downstream signaling pathways including gustducin, leading to GLP-2 release. GLP-2 acts on enteric neuron receptors (GLP-2R), transmitting signals to the basolateral side of small intestinal epithelial cells, where enteric neurons release neuropeptides that act on G protein-coupled receptors of absorptive epithelial cells, increasing intracellular cyclic adenosine monophosphate (cAMP) levels [24]. cAMP forms a cAMP-dependent complex with RNA-binding protein HuR and the 3' uridine-rich element (URE) in the mRNA non-coding region, regulating mRNA half-life and increasing SGLT1 mRNA stability to upregulate SGLT1 protein expression [25]. The body also regulates glucose-dependent SGLT1 expression through histone modifications. Studies show that high-starch/low-fat diets regulate SGLT1 expression at the transcriptional level through initial methylation of histone H3K4 and subsequent acetylation of H3/H4 [26]. Approximately two-thirds of newly synthesized SGLT1 protein exists in an intracellular SGLT1 pool, and its insertion into the membrane via exocytosis provides another protein-level regulatory mechanism for glucose absorption. Recent research has identified that RS1 protein (encoded by human RSC1A1 gene) contains multiple phosphorylation sites in its N-terminal domain; phosphorylation at different sites and binding to different receptors inhibits transport of various transporters to the membrane via exocytosis. When high luminal glucose is present, glucose inhibits RS1 binding to its receptor ornithine decarboxylase (ODC1) in the trans-Golgi network, reducing RS1' s inhibitory effect on SGLT1

vesicle release to the membrane and transiently upregulating SGLT1 protein expression [27].

3.2 Hormone Levels Hormones are crucial for maintaining systemic energy balance, regulating glucose synthesis, breakdown, and absorption to maintain blood glucose homeostasis. The SGLT1 promoter contains numerous transcription factor binding elements, including specificity protein 1 (SP-1), hepatocyte nuclear factor (HNF-1), nuclear factor-kappa B (NF- B) binding sequences, and cAMP response elements [28-29]. Epidermal growth factor (EGF) protects the intestine, enhances nutrient absorption, and reduces inflammatory responses. EGF binds to its receptor EGFR, activating intrinsic tyrosine kinase activity and downstream signaling pathways that phosphorylate cAMP response element-binding protein (CREB), which binds to the SGLT1 promoter to increase SGLT1 transcription. CREB may also play a key role in maintaining basal SGLT1 expression [30]. Lane et al. [31] added insulin-like growth factors (IGF) I and II to milk substitutes for newborn mice and found that IGF I and II significantly increased SGLT1 and GLUT2 mRNA expression in the mid-jejunum. IGF regulates SGLT1 through a pattern similar to EGF, binding to tyrosine kinase receptor IGF-IR to modulate SGLT1 gene expression [32]. Ghrelin increases SGLT1 and GLUT2 transcription levels through the growth hormone secretagogue receptor 1a (GHS-R1a) and phospholipase C (PLC) and protein kinase C (PKC) pathways [33]. The intestine possesses a relatively independent local renin-angiotensin system. Casselbrant et al. [34] found through pharmacological analysis that activation of angiotensin II (AngII) type 2 receptors enhanced SGLT1-mediated glucose absorption in jejunal mucosa, while type 1 receptor activation had inhibitory effects. Whether this regulation occurs through modulation of SGLT1 transcription and its regulatory pathways requires further investigation. Indeed, many hormones related to energy homeostasis (insulin, glucagon, and thyroid hormone) regulate intestinal glucose absorption by affecting SGLT1 transcription [35-36].

3.3 Inflammation Intestinal inflammation is a significant disease condition. In lipopolysaccharide (LPS)-induced systemic inflammation or sepsis models, downstream PKC and PKA signaling pathways are activated through NF- B and mitogen-activated protein kinase (MAPK) pathways (including three subfamilies: p38, ERK, and JNK), triggering a cascade of reactions that promote production of pro-inflammatory cytokines interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), as well as the mediator nitric oxide [37]. LPS, TNF-α, and IL-1β all inhibit glucose and galactose absorption. This inhibition involves PKC, PKA, MAPK, and NF- B pathways and proteasomal regulation of SGLT1. PKC reduces SGLT1 protein turnover rate and regulates endocytosis of SGLT1-containing vesicles; conversely, PKA activation increases SGLT1 protein transport rate, primarily affecting SGLT1 at the protein level and transport activity level [38]. It has also been reported that under inflammatory conditions, downregulation of SGLT1 gene expression is associated with

specific binding of SP-1 and HNF-1 to SGLT1 promoter elements [39].

3.4 Stress Under conditions of chronic psychological stress in rats and stress simulated by intraperitoneal dexamethasone injection in broiler chickens, GLUT2 protein and mRNA levels increase significantly in the apical membrane of jejunal epithelial cells, while SGLT1 maximal transport rate and mRNA levels decrease significantly without changes in protein level [40-41]. In contrast, Shepherd et al. [42] reported that in models of environmental stress and dexamethasone-induced stress, GLUT2 protein expression was inhibited in rat intestinal epithelial cell apical membranes, paradoxically accompanied by increased expression of PKCβII involved in GLUT2 translocation. Additionally, growing pigs under chronic heat stress showed increased SGLT1 mRNA expression in the duodenum and jejunum [43]. In Ebrahimi et al.' s report [44], lead-induced oxidative stress in broiler chickens significantly reduced both SGLT1 and GLUT2 mRNA expression. Different animal species and stressors may reflect different stress mechanisms. Typically, under stress conditions, the hypothalamic-pituitary-adrenal axis is activated, releasing glucocorticoids. Glucocorticoids primarily promote glucose production and absorption. Reichardt et al. [45] reported that glucocorticoids upregulate SGLT1, serum- and glucocorticoid-inducible kinase 1 (SGK1), and Na+/H+ exchanger 3 gene expression primarily through glucocorticoid receptor (GR) dimerization and binding to promoter elements. SGK1 mediates glucocorticoid-dependent upregulation of SGLT1 protein by inhibiting its ubiquitin-mediated degradation [46], while Na+/H+ exchanger 3 is related to SGLT1 transport activity. In summary, under stress conditions, reducing SGLT1-mediated energy-consuming glucose transport while increasing GLUT2-mediated facilitative transport is beneficial for animals.

3.5 Intestinal Environment The intestine is the site of nutrient digestion and absorption, and its internal environment directly affects epithelial glucose absorption. α-Amylase is the major pancreatic protease and starch hydrolase that specifically binds to highly glycosylated brush border membrane glycoprotein ligands in the duodenum, including sucrase-isomaltase and SGLT1. Binding of α-amylase to sucrase-isomaltase accelerates starch digestion to produce large amounts of glucose. However, high concentrations of α-amylase binding to SGLT1 inhibit glucose absorption, possibly due to steric hindrance [47], but this inhibition is transient as α-amylase is internalized via endocytosis and degraded by lysosomes, relieving the inhibition [48]. This transient inhibition of glucose absorption may have two physiological significances: avoiding rapid starch digestion that would sharply increase blood glucose, and providing amino acids to cells through lysosomal degradation of internalized α-amylase. SGLT1 transport is Na+- and voltage-dependent, so electrolyte and acid-base balance in the intestine necessarily affects its function. Kane et al. [49] found that SGLT1 affinity for glucose increases with pH. Intestinal microorganisms are part of intestinal function, and alterations in microbial flora also affect absorption capacity.

Diao et al. [50] found significant differences in gut microbiota at the genus level between different pig breeds, leading to changes in intestinal morphology and SGLT1 expression.

3.6 Other Factors SGLT1 expression is also affected by circadian rhythm. Fatima et al. [51] found that SGLT1 and GLUT2 protein levels in mouse small intestine peaked at 03:00-09:00. This physiological rhythm may be related to clock genes that regulate SGLT1 promoter regions through positive and negative feedback loops to maintain a 24-hour cycle [52]. SGLT1 expression is also related to animal developmental stage. Additionally, surgeries for treating obesity and type 2 diabetes, such as duodenal-jejunal bypass, gastrojejunostomy, sleeve gastrectomy, jejunum-ileum bypass, and ileectomy, adaptively alter SGLT1 and GLUT2 expression in intestinal epithelial cells [53-54]. Among these, ileectomy regulates SGLT1 and GLUT2 expression through downstream signaling pathways involving increased aldosterone secretion [55]. Environmental factors also affect intestinal morphology and function; Yalcin et al. [56] reported that egg storage duration before incubation and incubation temperature affect SGLT1 expression during chick development.

4 Summary

Intestinal glucose transport is a critical factor in glucose absorption and metabolism and serves as a drug target for regulating blood glucose stability and treating obesity and hyperglycemia. To adapt to intestinal and environmental stimuli, the body regulates SGLT1 and GLUT2 expression in the apical membrane of intestinal epithelium at transcriptional, mRNA, and protein levels. However, the molecular mechanisms of signaling pathways and regulatory levels for each factor remain unclear and require further investigation. Structural features are fundamental to SGLT1 and GLUT2 function, but direct crystal structures of SGLT1 and GLUT2 have not been obtained, with structural information derived from their homologs. Additionally, whether glucose transporter regulation can enhance luminal glucose digestion and utilization and modulate systemic glucose balance at the molecular level represents a future direction for molecular nutrition research. In conclusion, understanding the mechanisms of action and regulation of intestinal epithelial glucose transporters has both theoretical significance and practical implications for precise control of animal nutrition processes.

References

[1] FENG L, FROMMER W B. Structure and function of semisweet and sweet sugar transporters[J]. Trends in Biochemical Sciences, 2015, 40(8): 480–486.

[2] CHEN L Q, CHEUNG L S, FENG L, et al. Transport of sugars[J]. Annual Review of Biochemistry, 2015, 84(1): 865–894.

[3] MUECKLER M, THORENS B. The (GLUT) family of membrane transporters[J]. Molecular Aspects of Medicine, 2013, 34(2/3): 121–138.

[4] WRIGHT E M, LOO D D, HIRAYAMA B A. Biology of human sodium glucose transporters[J]. Physiological Reviews, 2011, 91(2): 733–794.

[5] FAHAM S, WATANABE A, BESSERER G M, et al. The crystal structure of a sodium galactose transporter reveals mechanistic insights Na+/sugar symport[J]. Science, 2008, 321(5890): 810–814.

[6] SALA-RABANAL M, HIRAYAMA B A, LOO D D, et al. Bridging the gap between structure kinetics human SGLT1[J]. American Journal Physiology Physiology, 2012, 302(9): C1293–C1305.

[7] YANG C B, ALBIN D M, WANG Z R, et al. Apical Na+-D-glucose cotransporter 1 (SGLT1) activity and protein abundance are expressed along the jejunal crypt-villus axis in the neonatal pig[J]. American Journal Physiology: Gastrointestinal Liver Physiology, 2010, 300(1): G60–G70.

[8] EROKHOVA L, HORNER A, OLLINGER N, et al. The sodium glucose cotransporter SGLT1 is an extremely efficient facilitator of passive water transport[J]. Journal of Biological Chemistry, 2016, 291(18): 9712–9720.

[9] SUN L F, ZENG X, YAN C Y, et al. Crystal Structure of a bacterial homologue of glucose transporters GLUT1–4[J]. Nature, 2012, 490(7420): 361–366.

[10] THORENS B. GLUT2, glucose sensing glucose homeostasis[J]. Diabetologia, 2015, 58(2): 221–232.

[11] CORPE C P, ECK P, WANG J, et al. Intestinal dehydroascorbic acid (DHA) transport mediated by the facilitative sugar transporters, GLUT2 and GLUT8[J]. Journal of Biological Chemistry, 2013, 288(13): 9092–9101.

[12] CHEN L H, TUO B G, DONG H. Regulation of intestinal glucose absorption by ion channels and transporters[J]. Nutrients, 2016, 8(1): 43–53.

[13] RÖDER P V, GEILLINGER K E, ZIETEK T S, et al. The role of SGLT1 and GLUT2 in intestinal glucose transport and sensing[J]. Plos One, 2014, 9(2): e89977.

[14] KUHRE R E, FROST C R, SVENDSEN B, et al. Molecular mechanisms glucose-stimulated GLP-1 secretion perfused small intestine[J]. Diabetes, 2015, 64(2): 370–382.

[15] MARGOLSKEE R F, DYER J, KOKRASHVILI Z, et al. T1R3 and gustducin in gut sense sugars to regulate expression of Na+-glucose cotransporter 1[J]. Proceedings of the National Academy of Sciences of the United States of America, 2007, 104(38): 15075–15080.

[16] KUHRE R E, BECHMANN L E, ALBRECHTSEN N J W, et al. Glucose stimulates neurotensin secretion from the rat small intestine by mechanisms in-

volving SGLT1 and GLUT2, leading to cell depolarization and calcium influx[J]. American Journal of Physiology: Endocrinology and Metabolism, 2015, 308(12): E1123-E1130.

[17] EGEROD K L, ENGELSTOFT M S, GRUNDDAL K V, et al. A major lineage of enteroendocrine cells coexpress CCK, secretin, GIP, GLP-1, PYY, and neurotensin somatostatin[J]. Endocrinology, 2012, 153(12): 5782-5795.

[18] YAN N. Structural advances the major facilitator superfamily (MFS) transporters[J]. Trends in Biochemical Sciences, 2013, 38(3): 151-159.

[19] AFFLECK J A, HELLIWELL P A, KELLETT G L. Immunocytochemical detection of GLUT2 intestinal brush-border membrane[J]. Journal Histochemistry & Cytochemistry, 2003, 51(11): 1567-1574.

[20] KELLETT G L, BROT-LAROCHE E, MACE O J, et al. Sugar absorption in the intestine: the role of GLUT2[J]. Annual Review of Nutrition, 2008, 28(1): 35-54.

[21] MORAN A W, AL-RAMMAHI M A, ARORA D K, et al. Expression of Na+/glucose co-transporter 1 (SGLT1) in the intestine of piglets weaned to different concentrations of dietary carbohydrate[J]. British Journal of Nutrition, 2010, 104(5): 647-655.

[22] COHEN M, KITSBERG D, TSYTKIN S, et al. Live imaging of GLUT2 glucose-dependent trafficking and its inhibition in polarized epithelial cysts[J]. Open Biology, 2014, 4(7): 140091.

[23] HELLIWELL P A, RUMSBY M G, KELLETT G L. Intestinal sugar absorption is regulated by phosphorylation and turnover of protein kinase C βII mediated by phosphatidylinositol 3-kinase-and mammalian target of rapamycin-dependent pathways[J]. Journal of Biological Chemistry, 2003, 278(31): 28644-28653.

[24] SHIRAZI-BEECHEY S P, MORAN A W, BATCHELOR D J, et al. Glucose sensing and signalling; regulation intestinal glucose transport[J]. Proceedings the Nutrition Society, 2011, 70(2): 185-193.

[25] LOFLIN P, LEVER J E. Hur binds a cyclic nucleotide-dependent, stabilizing domain in the 3' untranslated region Na+/glucose cotransporter (SGLT1) mRNA[J]. FEBS Letters, 2001, 509(2): 267-271.

[26] INOUE S, HONMA K, MOCHIZUKI K, et al. Induction of histone H3K4 methylation at the promoter, enhancer, and transcribed regions of the Si and Sglt1 genes in rat jejunum in response to a high-starch/low-fat diet[J]. Nutrition, 2015, 31(2): 366-372.

[27] CHINTALAPATI C, KELLER T, MUELLER T D, et al. Protein Rs1 (RSC1A1) downregulates the exocytotic pathway of glucose transporter SGLT1 at low intracellular glucose via inhibition of ornithine decarboxylase[J]. Molecular Pharmacology, 2016, 90(5): 508-521.

[28] MARTÍN M G, WANG J, SOLORZANO-VARGAS R S, et al. Regulation of the human Na+-glucose cotransporter gene, SGLT1, by HNF-1 and Sp1[J]. American Journal of Physiology Gastrointestinal & Liver Physiology, 2000, 278(4): G591-G603.

[29] LEE H M, LEE O H, KIM K J, et al. Ginsenoside Rg1 promotes glucose uptake through activated pathway insulin-resistant muscle cells[J]. Phytotherapy Research, 2012, 26(7): 1017-1022.

[30] WANG C W, CHANG W L, HUANG Y C, et al. An essential role of camp response element-binding protein in epidermal growth factor-mediated induction of sodium/glucose cotransporter 1 gene expression and intestinal glucose uptake[J]. The International Journal of Biochemistry & Cell Biology, 2015, 64: 239-251.

[31] LANE R H, DVORAK B, MACLENNAN N K, et al. IGF alters jejunal glucose transporter expression and serum glucose levels in immature rats[J]. American Journal of Physiology: Regulatory Integrative and Comparative Physiology, 2002, 283(6): R1450-R1460.

[32] JANKU F, HUANG H J, ANGELO L S, et al. A kinase-independent biological activity for insulin growth factor-1 receptor (IGF-1R): implications inhibition of IGF-1R signal[J]. Oncotarget, 2013, 4(3): 463-473.

[33] BLANCO A M, BERTUCCI J I, RAMESH N, et al. Ghrelin facilitates GLUT2-, SGLT1- and SGLT2-mediated intestinal glucose transport in goldfish (Carassius Auratus)[J]. Scientific Reports, 2017, 7: 45024.

[34] CASSELBRANT A, MALINAUSKAS M, MARSCHALL H U, et al. Angiotensin exerts dual actions on sodium-glucose transporter -mediated transport in the human jejunal mucosa[J]. Scandinavian Journal of Gastroenterology, 2015, 50(9): 1068-1075.

[35] LI Z W, SUN F, ZHANG Y H, et al. Tacrolimus induces insulin resistance and increases the glucose absorption in the jejunum: a potential mechanism of the diabetogenic effects[J]. PLoS One, 2015, 10(11): e0143405.

[36] MATOSIN-MATEKALO M, MESONERO J E, DELEZAY O, et al. Thyroid hormone regulation the Na+/glucose cotransporter SGLT1 in Caco-2 cells[J]. Biochemical Journal, 1998, 334(3): 633-640.

[37] 吴疑, 匡梅, 周红, 等. TLR4 信号通路及其负调控研究进展 [J]. 现代医药卫生, 2016, 32(18): 2821-2824.

[38] BARRENETXE J, SÁNCHEZ O, BARBER A, et al. TNFα regulates sugar transporters in the human intestinal epithelial cell line Caco-2[J]. Cytokine, 2013, 64(1): 181-187.

[39] KEKUDA R, SAHA P, SUNDARAM U. Role of Sp1 and HNF1 transcription factors in SGLT1 regulation during chronic intestinal inflammation[J].

American Journal of Physiology: Gastrointestinal and Liver Physiology, 2008, 294(6): G1354-G1361.

[40] BOUDRY G, CHEESEMAN C I, PERDUE M H. Psychological stress impairs Na+-dependent glucose absorption and increases GLUT2 expression in the rat jejunal brush-border membrane[J]. American Journal of Physiology: Regulatory, Integrative and Comparative Physiology, 2006, 292(2): R862-R867.

[41] LI Y, CAI H Y, LIU G H, et al. Effects of stress simulated by dexamethasone on jejunal glucose transport in broilers[J]. Poultry Science, 2009, 88(2): 330-337.

[42] SHEPHERD E J, HELLIWELL P A, MACE O J, et al. Stress and glucocorticoid inhibit apical GLUT2-trafficking and intestinal glucose absorption in rat small intestine[J]. Journal of Physiology, 2004, 560(1): 281-290.

[43] CERVANTES M, COTA M, ARCE N, et al. Effect of heat stress on performance and expression of selected amino acid and glucose transporters, Hsp90, leptin and ghrelin in growing pigs[J]. Journal of Thermal Biology, 2016, 59: 69-76.

[44] EBRAHIMI R, JAHROMI M F, LIANG J B, et al. Effect of dietary lead on intestinal nutrient transporters expression broiler chickens[J]. Biomed Research International, 2015, 2015: 149745.

[45] REICHARDT S D, FÖLLER M, REXHEPAJ R, et al. Glucocorticoids enhance intestinal glucose uptake dimerized glucocorticoid receptor enterocytes[J]. Endocrinology, 2012, 153(4): 1783-1794.

[46] GRAHAMMER F, HENKE G, SANDU C, et al. Intestinal function of gene-targeted mice lacking serum-and glucocorticoid-inducible kinase[J]. American Journal Physiology: Gastrointestinal and Liver Physiology, 2006, 290(6): 1114-1123.

[47] ASANUMA-DATE K, HIRANO Y, LE N, et al. Functional regulation of sugar assimilation By N-glycan-specific interaction of pancreatic α-amylase with glycoproteins of duodenal brush border membrane[J]. Journal of Biological Chemistry, 2012, 287(27): 23104-23118.

[48] DATE K, SATOH A, IIDA K, et al. Pancreatic α-amylase controls glucose assimilation by duodenal retrieval through N-glycan-specific binding, endocytosis, and degradation[J]. Journal of Biological Chemistry, 2015, 290(28): 17439-17450.

[49] KANE S, SEATTER M J, GOULD G W. Functional studies of human GLUT5: effect of pH on substrate selection and an analysis of substrate interactions[J]. Biochemical and Biophysical Research Communications, 1997, 238(2): 503-505.

[50] DIAO H, YAN H L, XIAO Y, et al. Intestinal microbiota could transfer host gut characteristics from pigs to mice[J]. BMC Microbiology, 2016, 16(1):

238.

[51] FATIMA J, IQBAL C W, HOUGHTON S G, et al. Hexose transporter expression and function in mouse small intestine: role of diurnal rhythm[J]. Journal of Gastrointestinal Surgery, 2009, 13(4): 634-641.

[52] BALAKRISHNAN A, STEARNS A T, ASHLEY S W, et al. Per1 modulates SGLT1 transcription vitro independent E-Box status[J]. Digestive Diseases Sciences, 2012, 57(6): 1525-1536.

[53] CAVIN J B, COUVELARD A, LEBTAHI R, et al. Differences in alimentary glucose absorption and intestinal disposal of blood glucose after roux-En-Y gastric bypass vs sleeve gastrectomy[J]. Gastroenterology, 2016, 150(2): 454-464.e9.

[54] WANG Y M, ZHANG X, LIU T, et al. Jejunum-ileum circuit procedure improves glucose metabolism in diabetic rats independent of weight loss[J]. Obesity, 2016, 24(2): 342-351.

[55] KHACHAB M, KANAAN A, AWAD D, et al. Colectomy induces an aldosterone-mediated increase in jejunal glucose uptake in rats[J]. Life Sciences, 2017, 174: 43-49.

[56] YALCIN S, GURSEL I, BILGEN G, et al. Effect of egg storage duration and brooding temperatures on chick growth, intestine morphology and nutrient transporters[J]. Animal: An International Journal of Animal Bioscience, 2017, 11(10): 1791-1797.

Note: Figure translations are in progress. See original paper for figures.