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Transepithelial Transports of Rare Sugar D-Psicose in Human Intestine

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ABSTRACT: D-Psicose (Psi), the C3-epimer of D-fructose (Fru), is a noncalorie sugar with a lower glycemic response. The trans-cellular pathway of Psi in human enterocytes was investigated using a Caco-2 cell monolayer. The permeation rate of Psi across the monolayer was not affected by the addition of phlorizin, an inhibitor of sugar transporter SGLT1, whereas it was accelerated by treatment with forskolin, a GLUT5-gene inducer, clearly showing that GLUT5 is involved in the transport of Psi. The permeability of Psi was suppressed in the presence of D-glucose (Glc) and Fru, suggesting that the three monosaccharides are transported via the same transporter. Since GLUT2, the predominant sugar transporter on the basolateral membrane of enterocytes, mediates the transport of Glc and Fru, Psi might be mediated by GLUT2. The present study shows that Psi is incorporated from the intestinal lumen into enterocytes via GLUT5 and is released to the lamina propria via GLUT2.

KEYWORDS: *Caco-2, rare sugar, GLUT5, GLUT2*

INTRODUCTION

Rare sugars, as defined by the International Society of Rare Sugars, are monosaccharides and their derivatives that are rare in nature. Izumori's research group succeeded in effective mass production of rare sugars using D-tagatose 3-epimerase (EC:5.3.1.-) derived from *Pseudomonas cichorii*, which catalyzes C3 epimerization of various ketohexoses.[1,2] The establishment of a large-scale production method of rare sugars has permitted thorough investigation of the biological functions of rare sugars and the potential for their application in the pharmaceutical, agricultural, and food industries. Accumulating data have shown vast possibilities for their applications.[3−7] In particular, D-psicose (Psi), the C3-epimer of D-fructose, is the fastest and most feasible candidate for application to food. D-Psicose, which has 70% of the sweetness of sucrose and no calories, is now utilized as a functional sugar with several health benefits, such as the prophylaxis of the development of diabetes.[8] Sun et al.[9,10] also reported that custard pudding and sponge cake containing Psi exhibit higher antioxidant activities and more favorable visco-elastic properties than those containing sucrose and D-fructose (Fru). Because of the health benefits and food properties that are suitable for food processing, much attention has been paid to Psi. D-Psicose was approved as generally recognized as safe (GRAS) by the US Food and Drug Administration in 2011.[11] An application for approval of the use of D-Psicose, with the suppressive effect against after-meal blood glucose elevation, as a food product for Specified Health Uses (FOSHU) has been made to the Japanese Ministry of Health, Labour, and Welfare.

D-Psicose is absorbed in the human small intestine, but it is not metabolized.[12] Most of Psi absorbed is excreted in the urine without being metabolized. Although the metabolic behavior of Psi is distinctly different from that of Fru, both of the two sugars are absorbed in the small intestine. The difference in metabolism and the similarity in absorption led us to the investigation of the absorption pathway of Psi in human intestine. A Caco-2 cell line derived from human colon carcinoma can spontaneously differentiate into the small intestinal epithelium.[13] The differentiated Caco-2 monolayer has a highly functionalized epithelial barrier, which contains tight junctions, microvilli, brush border enzymes and transporters.[14,15] Thus, the differentiated Caco-2 monolayer cultured on semipermeable membranes has been widely used in the assessment of absorption of nutrients. In this study, we investigate the trans-cellular transport pathway of Psi in human intestine using Caco-2 cell monolayer.

MATERIALS AND METHODS

Materials. The Caco-2 cell line (Cells of passage number, 43) was obtained from RIKEN BRC Cell Bank (Ibaraki, Japan). Dulbecco's modified eagle medium (DMEM) was purchased from Nissui Pharmaceutical Co. Ltd. L-Glutamine, nonessential amino acids (NEAA), and heat-inactivated fetal bovine serum (FBS) were purchased from Life Technologies Japan (Tokyo, Japan). Penicillin, streptomycin, and trypsin-EDTA solutions, and Sepasol-RNA I Super

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G were obtained from Nacalai tesque (Kyoto, Japan). D-Psicose (Psi) was obtained from the Rare Sugar Research Center, Kagawa University. D-Glucose (Glc), D-fructose (Fru), phlorizin (PZ), forskolin (FK), and Hank's buffered salt solution with phenol red (HBSS) were purchased from Wako Pure Chemical Industries (Osaka, Japan). Cell counting kit-8 (CCK-8) was obtained from Dojindo Laboratories (Kumamoto, Japan). Takara RNA PCR Kit AMV ver.3 and SYBR *Premix Ex TaqII* (Perfect Real Time) were purchased from Takara Bio Inc. (Shiga, Japan). BD Falcon 12-well cell culture inserts with transparent PET membrane filters (pore size: 1.0 μm) and their companion plates were purchased from Becton, Dickinson and Company, NJ, USA. Unless specified otherwise, all other chemicals used were guaranteed reagent grade.

Cell Culture. Caco-2 cells were routinely grown in 25 cm^2-CellBIND flasks (Corning Japan, Tokyo, Japan) using a maintenance medium, namely, DMEM medium supplemented with 20% (v/v) FBS, 1% (w/v) NEAA, 1% (w/v) L-glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin. They were seeded at 1.0×10^6 cells per flask at 37 °C, in an atmosphere of 95% air and 5% CO_2. The Caco-2 cells, grown to confluence in flasks, were trypsinized with a solution containing 0.25% (w/v) trypsin and 1 mM EDTA and washed twice in the maintenance medium.

Cell Viability Assay. Caco-2 cells were seeded at 4×10^4 cells/cm^2 in each well of a flat-bottom 96 well plate. They were cultured in the maintenance medium for 14 days at 37 °C in a CO_2 incubator (5% CO_2/95% air atmosphere) to be differentiated to a small intestine epithelium-like structure. The maintenance medium was changed every other day. Glc and Psi were dissolved in the medium to yield given concentrations (0.10 to 1.0×10^3 mM). One hundred microliters of the medium containing sugar was added to each well in which the Caco-2 cells had been cultured for 14 days. The Caco-2 cells in the presence of sugar were incubated at 37 °C for 48 h. At the end of the incubation period, the cells were washed with HBSS. The number of viable cells in each well was determined by WST-8 assay using CCK-8. The washed cells were incubated with 100 μL of maintenance medium and 10 μL of CCK-8 solution at 37 °C for 1 h. Absorbance at 450 nm was determined with a microplate reader. The observed absorbance units were converted to the number of viable cells using a conversion factor derived from a standard curve of the known number of viable Caco-2 cells.

Transport Studies. *Transepithelial Transport of Sugars Was Determined by Measuring the Amount of Sugar Permeated Across the Caco-2 Cell Monolayer Grown on a Transparent PET Membrane Filter.* Caco-2 cells (passage number, 66 to 79) were used in this experiment. Two milliliters of the maintenance medium was placed in the wells of 12-well cell culture insert companion plates. One milliliter of Caco-2 cell suspension was placed in the wells to get 4×10^4 cells/cm^2 in each of cell culture inserts with transparent PET membrane filters. The cell culture inserts were set into the wells of the plates. The cell culture inserts corresponded to the apical side of the Caco-2 cell monolayer, that is, apical chambers, and wells in their companion plates corresponded to the basolateral side of intestinal epithelium, that is, basolateral chambers. The Caco-2 cells in the apical chambers set into the basolateral chambers were cultured for 21 days at 37 °C in a 5% CO_2/95% air atmosphere. The media in the apical and basolateral chambers were changed every other day. After culturing for 21 days, the integrity of the Caco-2 cell layer was evaluated by measuring the transepithelial electrical resistance (TEER) with a Millicell-electrical resistance system (Millipore, MA, USA). The apical and basolateral chambers were rinsed three times with HBSS followed by a TEER measurement. The slots showing TEER values of more than 250 $\Omega\,cm^2$ were employed for the evaluation of transepithelial transport of sugars.

The apical and basolateral chambers were rinsed once with 20 mM HEPES buffer (pH 7.5) supplemented with 137 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, and 1.8 mM $CaCl_2$. The apical and basolateral chambers were filled with 0.5 and 2.0 mL of HEPES buffers, respectively. The apical chambers were reset in the basolateral chambers, and preincubated for 30 min at 37 °C in a 5% CO_2/95% air atmosphere. Following the preincubation, sugar solutions with a concentration of each sugar of 60 mM (Glc, Fru, and/or Psi) dissolved in HEPES buffers (0.5 mL) were added to the apical chambers (final concentration of each sugar added, 30 mM). After an incubation period of 0, 30, 60, and 120 min, samples (0.4 mL) were collected from the basolateral chambers and the same volume of HEPES buffer was immediately added to refill the basolateral chambers. The TEER values of the Caco-2 cell monolayer were measured every 30 min. After the 120 min incubation, samples (0.4 mL) were collected from the apical chambers. All the solutions recovered were subjected to the sugar analysis described below.

Sugar Transport Was Examined in the Presence of a SGLT1 Inhibitor. Sugar transport across the Caco-2 monolayer was evaluated in the presence of PZ, a SGLT1 inhibitor. After the apical and basolateral chambers were rinsed once with HBSS, 1.0 and 2.0 mL of HBSSs were added to the chambers, respectively. After being set in the basolateral chambers, the apical chambers were preincubated for 30 min at 37 °C in a 5% CO_2/95% air atmosphere. Then, the fluids in the apical chambers were removed and 0.5 mM PZ solutions (0.5 mL) dissolved in HBSS were added to the apical chambers. After a 2 min preincubation in a CO_2 incubator, 0.5 mL of 200 mM sugar solutions (Glc, Fru, or Psi) dissolved in HBSS was added to the apical chambers (final concentration of sugar added, 100 mM). At 0, 30, 60, and 120 min after application of the sugar solutions, the samples (0.4 mL) were collected from the basolateral chambers. The procedures after the sample recovery were performed as described above.

Sugar Transport Was Examined Using a GLUT5-Overexpressing Caco-2 Monolayer Prepared by Pretreatment with FK, a GLUT5-Gene Inducer. An FK stock solution (FK concentration, 50 mM) was prepared by dissolving in 99.5% ethanol. The FK stock solution was added to the maintenance medium to yield a final FK concentration of 50 μM. The apical and basolateral chambers, cultured with maintenance media for 18 days, were filled with 1.0 and 2.0 mL of the maintenance media containing 50 μM FK, respectively. After culturing for 2 days, the media in the chambers were replaced by fresh media containing 50 μM FK and incubated for one day in the CO_2 incubator. After once rinsing with HBSS, the apical and basolateral chambers were filled with 0.5 and 2.0 mL of HBSS, respectively, and were preincubated at 37 °C in a 5% CO_2/95% air atmosphere. After a 30 min preincubation, 0.5 mL of 200 mM sugar solution (Glc, Fru, or Psi) dissolved in HBSS was added to each of the apical chambers (final concentration of sugar added, 100 mM). At 0, 30, 60, and 120 min after application of the sugar solutions, samples (0.4 mL) were collected from the basolateral chambers. The procedures after the sample recovery were performed as described above.

Sugar Analysis. Determination of Glc, Fru, and Psi was carried out by a post column HPLC system with pulsed amperometric detection (PCHPLC-PAD) as described by Oshima et al.[16] The sample solutions recovered from the apical and basolateral chambers were diluted four times with ultrapure water. The diluted sample solutions were filtered through 0.2 μm syringe filters (Minisart RC4; Sartorius Stedim Japan K.K.,Tokyo,Japan). Then, the sample pretreatment of the filtrate was done with a Sep-Pak C18 plus Light Cartridge (Waters, MI, USA) according to the manufacturer's instructions. The sample solutions, after the pretreatment, were further diluted 50 times for the apical samples and two times for the basolateral samples. The diluents were subjected to sugar analysis by PCHPLC-PAD. The PCHPLC-PAD analysis was performed on a Metrohm MIC-8 system (KMT-100MIC Compact auto sampler, 817 Bioscan PAD detector, 709 IC pump, 812 valve units; Metrohm Ltd., Herisau, Switzerland) with a GL-C611 column (10.7 mm i.d. × 300 mm; Hitachi Chemical Co., Tokyo, Japan). Twenty microliter aliquots of the diluted sample solutions were injected into the GL-C611 column and eluted with 0.1 mM NaOH at the flow rate of 1.0 mL/min (Column temperature, 60 °C). The effluent from the column was mixed with a 0.3 M NaOH solution at a flow rate 0.43 mL/min to perform the postcolumn derivatization for PAD analysis. The pulse potentials of PAD detector for detection of the reaction products and their durations were as follows: E_1 = 0.05 V (t_1 = 0.40 s), E_2 = 0.75 V (t_2 = 0.20 s), E_3 = −0.15 V (t_3 = 0.40 s) with the sample analysis time set to 0.10 s. The sugar

concentrations of samples were determined using the calibration curves of the standard sugars (Glc, Fru, and Psi).

Isolation of Total RNA and Real-Time PCR. Total RNA was extracted from the Caco-2 cells, which were treated with FK for 3 days after an 18-day incubation. The Caco-2 cells in the apical chamber were rinsed with PBS. RNA was isolated from the cells using Sepasol-RNA I Super G according to the manufacturer's instructions. Complementary DNA of the isolated RNA (2 μg) was synthesized using a Takara RNA PCR Kit AMV ver.3 according to the manufacturer's instructions. Real-time polymerase chain reaction (PCR) was conducted using SYBR *Premix Ex Taq*II (Perfect Real Time) on a Thermal Cycler Dice Real Time System TP800 (Takara Bio Inc.). The PCR conditions were an optimal 2-step protocol (40 cycle of 95 °C for 5 s and 60 °C for 30 s after denaturation at 95 °C for 30 s) as per the manufacturer's instructions. Forward and reverse PCR primers for human GLUT5 mRNA were 5′-TGGAGCAAC-AGGATCAGAGCATGA-3′ and 5′-ACATGGACACGGTTACAG-ACCACA-3′, respectively. Forward and reverse primers for human glyceraldehyde 3-phosphate dehydrogenase (GAPDH) mRNA as a housekeeping gene were 5′-ACTGGCGTCTTCACCACCAT-3′, and 5′-TCCACCACCCTGTTGCTGTA-3′, respectively. To estimate the relative gene expression, data obtained from real time PCR were analyzed by the comparative C_T method with the computer software Multiplate RQ (Takara Bio Inc.).

Statistics Analysis and Data Presentation. Values reported are the mean ± standard deviation (SD). The statistical significance of difference among the groups was determined by a Tukey test for multiple comparisons and by Student's *t*-test for pairwise comparisons. A difference with $P < 0.05$ was considered significant.

RESULTS AND DISCUSSION

Cytotoxicity of D-Psicose. Figure 1 shows the cytotoxicity of Psi in Caco-2 cells. Psi had little effect on cell viability of the Caco-2 cells at concentrations less than 1.0×10^2 mM, but the addition of 5.0×10^2 mM Psi resulted in a 30% decrease of the cell viability. The cell viability decreased up to 38% at 1.0×10^3 mM Psi. The most common carbohydrate, Glc, also showed a dose-dependent reduction in the viable cell number. 1.0×10^3 mM Glc induced a 53% fall in the cell number. The cytotoxicity level of Psi, similar to that of Glc, implies that the acute toxicity of Psi to intestine epithelial cells is as low as that of Glc.

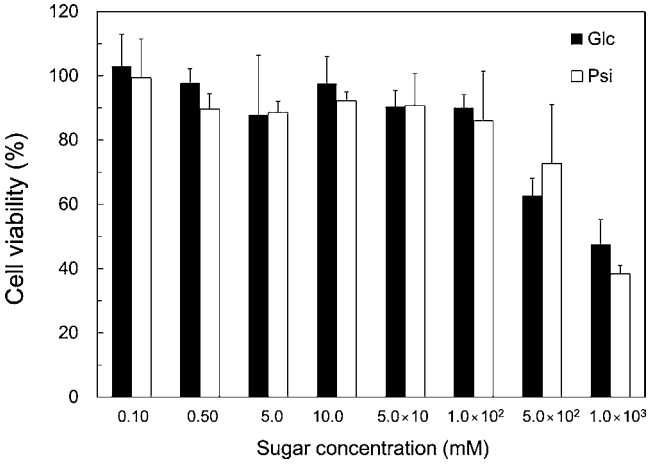

Figure 1. Effects of Psi on Caco-2 cell viability. Data are presented as mean value ± SD (n = 12).

Uptake Pathway of D-Psicose in the Apical Membranes of Human Enterocytes. Absorption of monosaccharides occurs primarily in the small intestine. Monosaccharides in the intestinal lumen are incorporated into the enterocyte via a sugar transporter located in the apical membrane and effluxed from the cell to the lamina propria via another sugar transporter located in the basolateral membrane. Uptake of Glc into small intestine epithelial cells is mediated mainly by a sodium dependent glucose cotransporter member 1 (SGLT1).[17] In contrast with Glc, Fru enters the enterocytes by a facilitated glucose transporter member 5 (GLUT5), also known as a fructose transporter.

The transcellular permeability of Glc, Fru, and Psi at the concentration of 100 mM was investigated using the Caco-2 cell monolayers of which SGLT1 and GLUT5 were modulated using chemical agents. TEER values of the monolayers were more than 250 $\Omega\,cm^2$ over the incubation time with 100 mM sugar (720−810 $\Omega\,cm^2$ at 0 min and 250−270 $\Omega\,cm^2$ at 120 min), suggesting that the monolayers maintain intestinal epithelial integrity. The amount of permeated Glc increased linearly with the incubation time (Figure 2a). The amount of permeated Glc after 120 min incubation reached 4000 $\mu g/cm^2$. In the presence of 0.25 mM PZ, Glc permeability was remarkably depressed. In particular, it was highly suppressed in the first 30 min. The permeated amount was only 25% of the amount in the absence of PZ. It is well-known that the coexistence of PZ suppresses the transcytosis of Glc in the intestinal epithelium since the flavonoid PZ inhibits the action of SGLT1 competitively.[18] Consequently, the depressed Glc permeation by PZ shows that the main transporter of Glc in the Caco-2 monolayer is SGLT1. The treatment of the Caco-2 monolayer with the GLUT5 inducer FK did not affect the permeability of Glc.

The permeation amount of Fru increased linearly with time, as did that of Glc (Figure 2b). However, the permeability level was half that of Glc. This may be due to the differences in the activity or expression level between the active sugar transporter SGLT1 and the facilitative sugar transporter GLUT5. In the presence of PZ, the permeated amount decreased to 40% in the first 60 min but recovered to 80% at the incubation time of 120 min. On the other hand, FK treatment of the Caco-2 cell monolayer resulted in a 4-fold increase in the permeability level. Mahraoui et al.[19] reported that treatment of the differentiated Caco-2 monolayer with 50 μM FK increased Fru uptake. FK stimulates adenylate cyclase and raises the intracellular cyclic AMP levels, resulting in elevations in GLUT5 mRNA (7-fold) and its protein levels (5-fold) respectively. GLUT5-over-expression on Caco-2 is thought to have facilitated the Fru uptake. Therefore, the present results affirm that GLUT5 participates in the Fru transport across the Caco-2 cell monolayer. Augustin[20] reported that GLUT7, a transporter of GLUT family, is also present in the apical side of the small intestine and can transport Fru. GLUT7 might be also involved in the transportation of Fru across the Caco-2 cell monolayer.

Psicose also permeated across the Caco-2 cell monolayer. The permeability rate of Psi was similar to that of Fru (Figure 2c). The presence of PZ lowered the permeability of Psi in the first 60 min, which is the same phenomenon as with Fru. The result that PZ transiently lowered the permeability of Psi and Fru might be due to the aglycone phloretin, produced from PZ by the action of enterocyte's glucosidases, which inhibits the transport of GLUT2.[21,22] FK treatment showed a more drastic change than the effect caused by PZ. The treatment of the Caco-2 monolayer with FK enhanced the permeation amount of Psi to 3.2-times after 120 min incubation. The permeability increase induced by FK treatment is due to either the expression-level elevation of GLUT5 on Caco-2 cell mem-

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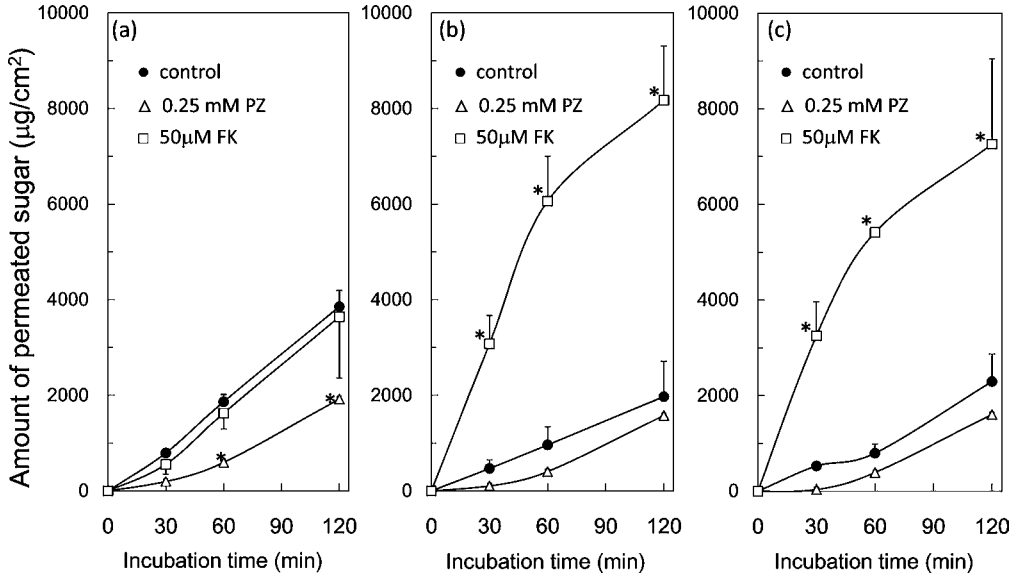

Figure 2. Effects of transporter inhibitor and inducer on apical-to-basolateral transport of (a) Glc, (b) Fru, and (c) Psi. The concentration of each sugar added was 100 mM. ●, control (HBSS alone, that is, without PZ and untreated with FK); Δ, in the presence of 0.25 mM PZ; and □, cell layer treated with 50 μM FK. Data are presented as mean value ± SD (n = 5). *Significance (P < 0.05) of difference among the groups was determined by Tukey test.

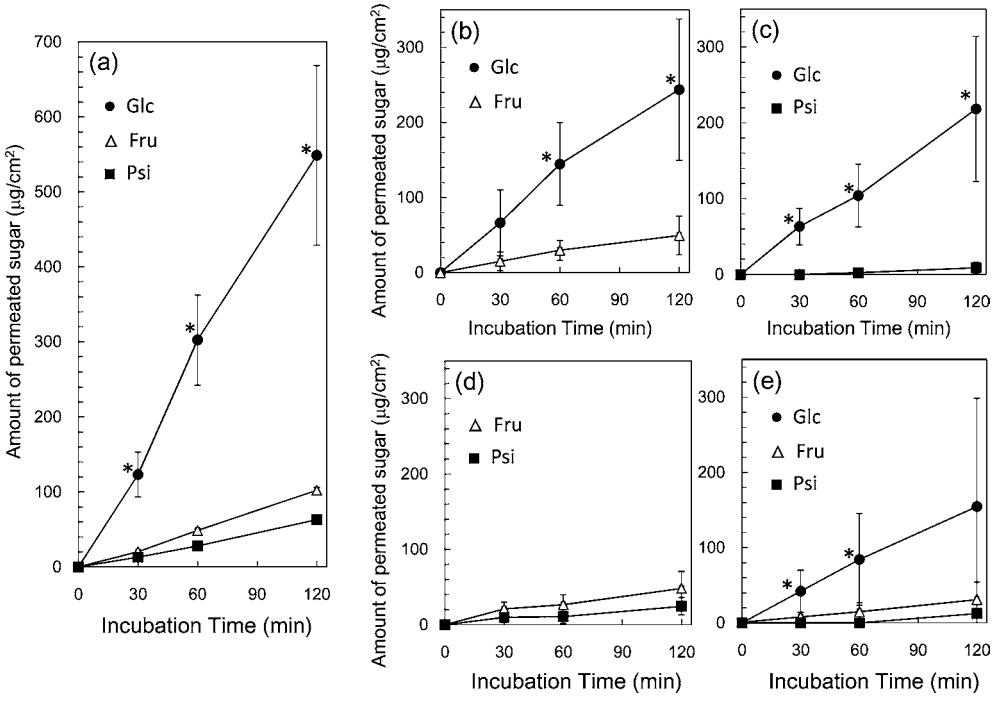

Figure 3. Apical-to-basolateral transport of mixed sugars across the Caco-2 cell monolayer; (a) a single sugar, (b) mixture of Glc and Fru, (c) mixture of Glc and Psi, (d) mixture of Fru and Psi, and (e) mixture of Glc, Fru, and Psi. ●, Glc (30 mM); Δ, Fru (30 mM); and ■, Psi (30 mM). Data are presented as mean value ± SD (n = 6). *Significance (P < 0.05) of difference among the groups was determined by Tukey test for multiple comparisons and by Student's t-test for pairwise comparisons.

branes or the elevation of the sugar transport activity of GLUT5.

The effects of FK treatment on GLUT5 expression of Caco-2 cells were investigated by real time-PCR. The relative quantity (crossing point) of GLUT5 mRNA in the FK-treated cells compared with control cells (1.00 ± 0.88, n = 4) was 5.00 ± 0.66 (n = 4), showing that the GLUT5-mRNA level increased 5-fold with FK treatment. Thus, we speculate that the accelerated Psi permeability by FK treatment was caused by the GLUT5 proteins overexpressed in the apical membrane of the Caco-2 cells. Although it has been reported that FK also induces the expression of other members of the GLUT family, such as GLUT1 and GLUT3, there is no report regarding the distribution of GLUT1 and GLUT3 on the brush border membrane of the small intestine.[23] It is conceivable that Psi is incorporated via the fructose transporter GLUT5 from the intestinal lumen into the intestinal enterocyte. Another fructose transporter GLUT7 existing on the brush border membrane of

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the small intestine may be also involved in the transport of Fru.[20]

Efflux of D-Psicose in the Basolateral Membranes of Human Enterocytes. GLUT2, a facilitated diffusion glucose transporter 2, is the predominant sugar transporter on the basolateral membrane of intestinal absorptive cells, and it transports D-glucose, D-galactose, D-mannose, and D-fructose.[17] However, it is unknown whether the transport of Psi takes place in GLUT2 on the basolateral membrane or not. If Psi is effluxed through GLUT2 on the basolateral membrane, Psi is to compete with other monosaccharides such as Glc and Fru for transportation at GLUT2. To examine whether Psi is effluxed via GLUT2 of the Caco-2 basolateral membrane, the permeability of two or three types of monosaccharides were analyzed using Caco-2 monolayers (Figure 3). The Caco-2 monolayers maintained intestinal epithelial integrity over the incubation time with sugars (the concentration of each sugar, 30 mM), as shown in the TEER values (549−563 $\Omega\,cm^2$ at 0 min incubation and 472−499 $\Omega\,cm^2$ at 120 min incubation).

When a single monosaccharide at 30 mM was added onto the Caco-2 monolayer, the permeated amount of each monosaccharide increased linearly with the incubation time (Figure 3a). The permeability of Psi was low compared with that of Glc and Fru. The permeated amount after 120 min incubation was 63 $\mu g/cm^2$, which was only 10% of Glc-permeation and 60% of Fru-permeation. This indicates that the absorption rate of Psi from the intestinal enterocyte is lower than that of Glc and Fru.

The two types of sugars were added together onto a Caco-2 monolayer. The sugar permeability of individual sugars at 30 mM is shown in Figure 3 b-d. The coexistence of Glc with Fru resulted in 44%-decrease in the permeation rate of Glc (Figure 3b). The permeation rate of Fru also decreased up to 51%. The decreases in the permeation rates of the two sugars can be ascribed to the competitive sugar efflux at the sugar transporter GLUT2 of the Caco-2 basolateral membrane since the influx routes of the two sugars are separate. The coexistence of Glc with Psi induced a 60% decrease in the Glc-permeability (Figure 3c). Furthermore, the amount of permeated Psi was 10 $\mu g/cm^2$ after 120 min, which was only 14% of Psi alone. These results are indicative of the competitive transport of the two sugars. A mixture solution of Fru and Psi lowered the permeation rate of individual sugars to approximately half (Figure 3d). The lowered permeation rate may be partially caused by the competitive influx of Fru and Psi at GLUT5 in the apical membrane.

The three types of sugars were added together onto a Caco-2 monolayer. The permeation amounts of individual sugars after 120 min incubation were 155, 30, and 13 $\mu g/cm^2$ for Glc, Fru, and Psi, respectively, which was below one-third of the permeation amount when only one type of sugar was added (Figure 3e). Despite the addition of each sugar at 30 mM, the drops in the permeability level suggest that competitive transport of three types of sugar occur in either influx at an apical transporter or efflux at a basolateral transporter. However, influx of Glc into intestinal enterocytes does not compete with that of Fru because the apical transporter of Glc differs from that of Fru.[17]

Thus, it is probable that in a sugar transporter on the basolateral membrane (i.e., GLUT2) these three sugars compete with one another. This would be consistent with the results of permeability of two types of sugars. To sum up, the efflux of Psi from the enterocytes might be conducted by facilitated diffusion via GLUT2. Psicose absorbed from the small intestine via the transporters GLUT5 and GLUT2 circulates in blood and performs several important biological functions including the improvement of insulin resistance and the inhibition of body fat accumulation.[24,25]

CONCLUSION

The permeation study of the monosaccharides using Caco-2 cell monolayers clearly showed that the noncalorie ketohexose D-psicose is incorporated from the intestinal lumen into the enterocytes via GLUT5 and possibly via GLUT7 located in the apical epithelial membrane and is released to the lamina propria via GLUT2 located in the basolateral membrane. The transport route of Psi was the same as that of Fru. Furthermore, the permeability was similar to that of Fru, suggesting that Psi has a relatively high internal absorption in the human intestine. We hypothesize that the similarity in behavior of Psi to Fru is due to the transporters GLUT5 and GLUT2 recognition of the two sugar molecules as similar molecules, because Psi has a structure similar to Fru under aqueous conditions.[26] It is interesting that, in spite of the difference in metabolism in the human body, Psi is absorbed in the same way that Fru is.

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Notes

The authors declare no competing financial interest.

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