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Research Communications

# Enhancement of sucrase-isomaltase gene expression induced by luminally administered fructose in rat jejunum

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*We have previously shown that feeding a diet containing sucrose to rats causes an elevation of sucrase-isomaltase (SI) mRNA level in the jejunum. In this study, we examined whether the SI mRNA level could be directly elevated by administration of one of the constituting monosaccharides (i.e., glucose and/or fructose). Gastric intubation of a sucrose solution caused increases in both sucrase activity and SI mRNA level in the jejunum. Intrajejunal intubation of fructose, but not glucose, led to an elevation of sucrase activity and SI mRNA level. To examine whether fructose directly affects the gene expression of SI at the segment where the absorption of this sugar takes place or the sugar-induced increase in the gene expression of SI is secondary to any possible changes in the level(s) of certain hormonal factor(s) in the blood stream, a solution containing either fructose or glucose was simultaneously perfused into two consecutive cannulated and irrigated loops of jejunum that were not isolated from blood circulation. Compared with the loop perfused with glucose, the loop perfused with fructose exhibited significantly greater sucrase activity and SI mRNA level as well as the elevated GLUT5 mRNA level. These results suggest that fructose is capable of directly increasing the gene expression of SI and GLUT5 in the confined segment where fructose is absorbed.* (J. Nutr. Biochem. 10:8–12, 1999) 

**Keywords:** sucrase-isomaltase; gene expression; fructose; GLUT5; rats

## Introduction

Sucrase-isomaltase (SI) is expressed in the brush-border membranes of small intestinal epithelial cells and plays a pivotal role in the digestion and absorption of carbohydrate.[1] Feeding a high-starch diet caused an elevation of SI mRNA levels in rat jejunum, and this diet-related increase in SI mRNA level was reported to be induced by the orogastric feeding of a sucrose diet within 12 hours.[2] However, previous studies concerning dietary regulation of SI gene expression were complicated by the inevitable change in the amount of fat or protein in the diet, both of which were shown to modify sucrase activity in the jejunum.[3–5] Furthermore, the possible involvement of certain humoral factor(s) in this diet-induced change in SI gene expression could not be excluded. To explore whether sucrose and its constituting monosaccharides are capable of directly stimulating the small intestinal epithelial cells to enhance the gene expression of SI, we compared the SI mRNA levels in the cannulated and irrigated loops of two consecutive jejunal segments that were simultaneously perfused with solutions containing glucose or fructose, respectively.

## Methods and materials

### *Animals and diets*

To investigate carbohydrate-induced increases in SI gene expression in rat jejunum, we performed three experiments with different techniques of administration of sugars: gastric intubation (force-feeding), intrajejunal intubation, and intrajejunal perfusion of sugar solutions.

It is well known that a minimal level of SI expression is reached within a few days following the introduction of an isoenergic low-carbohydrate (high-fat) diet.[6,7] To attain a basal low level of SI expression, 6-week-old male rats of Wistar strain (Japan SLC,

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Hamamatsu, Japan) were fed a low-starch (4.7% energy as corn starch), high-fat (72.7% energy as corn oil) diet[2] for 7 days, and then the animals were subjected to the following three experiments, which enabled us to investigate the effect of sugars on the gene expression of SI under the different physiologic conditions of rat jejunum. To standardize for the known diurnal rhythm of sucrase activity,[8] the rats were always euthanized between 4:00 PM and 5:00 PM.

**Gastric intubation.** During the last 6 hours after the 7-day period of the pre-feeding, rats were intubated into the stomach with the liquid low-starch, high-fat diet or an isocaloric liquid sucrose diet (40% energy as sucrose, 37% energy as corn oil, 22% energy as casein),[2] or they received the equivalent amount of sucrose in water (23.7%) using a polypropylene tube. These diets and the sucrose solution were given twice during the 6-hour period with 3-hour intervals. The volume of the diets and the solution was 1.61 mL/100 g body weight per intubation.

**Intrajejunal intubation.** Under anesthesia with pentobarbital (50 mg/kg body weight), the abdominal cavity was opened, and 2 mL of glucose-free and pyruvate-free Dulbecco's modified Eagle medium (DMEM; Sigma, St. Louis, MO USA) (control) or the medium containing either 292 mM glucose, 292 mM fructose, or 292 mM sucrose was injected into the jejunal lumen using a syringe and a needle (27 gauge). The animals were euthanized 6 hours later.

**Jejunal perfusion.** Perfusion of jejunal loops was performed according to the procedure described by Lambert.[9] Under anesthesia with pentobarbital (50 mg/kg body weight), incisions were made on the wall of the jejunum 15 cm and 23 cm distal to the ligament of Treitz, with care taken not to cut small vessels. Other incisions were made 24 cm and 32 cm distal to the ligament of Treitz, leading to isolation of two consecutive jejunal loops (8 cm each). A small cannula was introduced at each end of the loops, and then the two isolated loops were washed with DMEM by two cannulae. A silicone tubing attached to a rotory pump was connected to each cannula of the first loop, and a tubing of the second pump was connected to each cannula of the second loop. The two loops were perfused simultaneously with DMEM containing 200 mM glucose into one loop and 200 mM fructose into the other loop for 3 hours at a flow rate of 10 mL/hr. A 1-cm segment between the two consecutive loops was excised at the start of perfusion as a control segment. The remaining jejunoileal segment was end-to-end anastomosed.

All animals had unrestricted access to water. The experimental procedures used in the present study met the guidelines of the animal usage committee of the University of Shizuoka.

### *Preparation of intestinal samples*

In rats intubated gastrically or intrajejunally, the entire small intestine was removed and the duodenum extending from the pylorus to the ligament of Treitz was discarded. The jejunoileum was divided into three segments of equal length. The proximal third (jejunum) of the jejunoileum was flushed with ice-cold 0.9% sodium chloride (NaCl) solution. From rats subjected to the intestinal perfusion, the isolated jejunal loops were excised and the inside of the loops were flushed with ice-cold 0.9% NaCl. Of two 1-cm segments (100 mg each) excised from the middle region of the jejunal loops, one was immediately used for RNA extraction, and the other segment was homogenized in 4 volumes of ice-cold 10 mM potassium phosphate buffer (pH 7.0). The jejunal homogenate was used for assays of sucrase activity and total proteins.

### *Enzyme assays*

Sucrase activity was assayed as described by Dahlqvist,[10] with 28 mM sucrose as substrate. Protein was determined according to the method of Lowry et al.[11]

### *RNA extraction and Northern blot hybridization*

Total RNA was extracted as described by Chomczynski and Sacchi.[12] For Northern blot hybridization analysis, aliquots (20 μg) of total RNA were denatured with 2.2 M formaldehyde, fractionated by electrophoresis on 1% agarose gels, and transferred to a nylon membrane (Hybond-$N^+$, Amersham) as described previously.[2] The hybridization was performed using $^{32}$P-labeled rat SI cDNA as described previously.[2] The cDNA probe was labeled with [α-$^{32}$P]dCTP (3,000 Ci/mmol, ICN Biochemicals) using the random primer DNA labeling system (Takara Shuzo, Kyoto, Japan). The radioactivity on the membranes was analyzed with an image analyzer (BAS 2000, Fuji Film, Tokyo, Japan). Control hybridization was performed using a rat β-actin cDNA and a rat 28S rRNA cDNA. Because β-actin mRNA abundance relative to 28S rRNA was unaltered by the diets used in this study during the experimental periods (3 or 6 hours), the abundance of SI and GLUT5 mRNA was normalized for the β-actin mRNA.

### *Statistics*

All results were subjected to one-way analysis of variance. Differences in mean values among groups were tested using Tukey's multiple range test[13] or paired *t*-test, if applicable, and were considered statistically different at a *P*-value of less than 0.05.

## Results

### *Effect of orogastric feeding of sucrose on SI gene expression*

To examine whether a sucrose solution is able to elicit an increase in the gene expression of SI in the small intestine, we gastrically intubated the sucrose solution to the rats that had been fed a low-carbohydrate, high-fat diet. Sucrase activity in the jejunal homogenate of rats given the sucrose diet was significantly greater (71%; $P < 0.05$) than that of control. Gastric administration of the sucrose solution also caused a significant increase (124%; $P < 0.01$) in sucrase activity in the jejunum (*Figure 1*). The levels of SI mRNA in the jejunum were significantly elevated in rats fed the sucrose diet (149%) as well as in those given the sucrose solution (267%) when compared with the control (*Figure 1*).

### *Effect of intrajejunal intubation of sucrose on SI gene expression*

A direct injection of the sucrose solution or fructose solution into the jejunal lumen caused significant elevation of sucrase activity and SI mRNA level within 6 hours compared with those of the control (*Figure 2*). By contrast, intrajejunal injection of the glucose solution affected neither sucrase activity nor SI mRNA levels (*Figure 2*).

### *Effect of jejunal perfusion of glucose and fructose solutions on SI gene expression*

To examine whether the enhancement of SI gene expression was induced by the luminally administered fructose, we perfused the fructose and glucose solutions into the two consecutive jejunal loops. Sucrase activity in the jejunal loops perfused with the glucose solution and in those perfused with the fructose solution was 29% and 52%, respectively, greater than that of the adjacent segments obtained at the start of perfusion (control). Sucrase activity

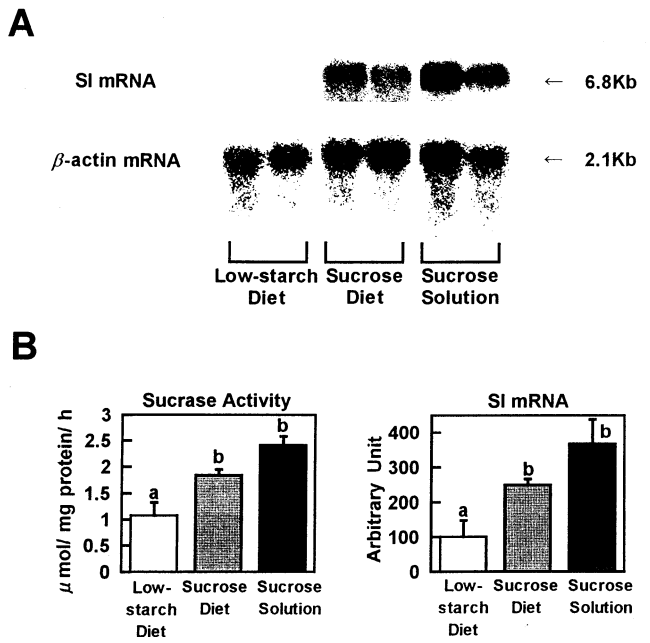


**Figure 1** Effects of gastric intubation of sucrose diet and sucrose solution on the sucrase activity and sucrase-isomaltase (SI) mRNA level in rat jejunum. Rats were force-fed the low-starch, high-fat diet (low-starch diet, control), sucrose diet, or sucrose solution for 6 hours. Total RNA was extracted from the jejunal segments of individual rats. Representative Northern blots for SI mRNA and β-actin mRNA are shown in *Figure 1A*. The results for each sample normalized for the β-actin mRNA abundance were expressed as arbitrary units, representing the mean value of the control group as 100% (*Figure 1B*). Results are expressed as means ± SEM for four animals per group. a,b: Values not sharing a common superscript are significantly different ($P < 0.05$) from one another by Tukey's multiple range test.

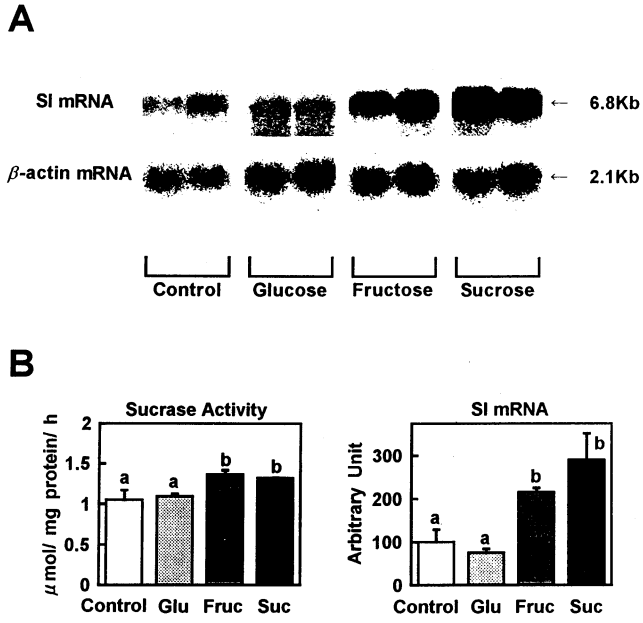


**Figure 2** Effects of intrajejunal intubation of glucose, fructose, and sucrose on the sucrase activity and sucrase-isomaltase (SI) mRNA level in rat jejunum. Rats were intrajejunally intubated with 2 mL of carbohydrate-free solution (control) or the solution containing 292 mM glucose, fructose, or sucrose 6 hours prior to euthanasia. Representative Northern blots for SI mRNA and β-actin mRNA are shown in *Figure 2A*. The results for each sample normalized for the β-actin mRNA abundance were expressed as arbitrary units, representing the mean value of the control group as 100% (*Figure 2B*). Results are expressed as mean ± SEM for four animals per group. a,b: Values not sharing a common superscript are significantly different ($P < 0.05$) from one another by Tukey's multiple range test.

in the loops perfused with the fructose solution was significantly greater ($P < 0.05$) than that of loops perfused with the glucose solution (*Figure 3*). The SI mRNA levels of the jejunal segments perfused with the fructose solution increased by 22% during the 3-hour perfusion period, and its levels were significantly greater ($P < 0.05$) than those of the segments perfused with the glucose solution (*Figure 3*). The GLUT5 mRNA level was unaltered in the segments perfused with the glucose solution, but it was significantly elevated (77%; $P < 0.05$) in the segments perfused with the fructose solution (*Figure 3*).

## Discussion

The present study has shown that sucrase activity and SI mRNA level in the jejunum were coordinately increased within 6 hours after the force-feeding of a sucrose diet. This result is consistent with previous studies that showed that force-feeding a sucrose diet to rats caused rapid increases in the sucrase activity and immunoreactive SI protein,[14,15] as well as the enhancement of SI mRNA levels[2,16] in the jejunum. By comparing the effect of the sucrose diet with that of the sucrose solution, we showed that sucrose was able to increase SI mRNA abundance regardless of the presence or absence of other nutrients. This result strongly suggested that the increase in SI gene expression observed in the rats given a sucrose diet was mainly ascribed to the sucrose in the diet. This was further confirmed by the finding that direct injection of the sucrose solution into the jejunal lumen caused increases in both sucrase activity and SI mRNA level. In this study, we found that, of the two constituting monosaccharides of sucrose, only fructose was active in enhancing SI mRNA levels in the jejunum (*Figure 2*). Therefore, it was most likely that the sucrose-induced increase in SI mRNA levels was attributable to fructose, which was produced by the hydrolysis of sucrose. However, we were yet uncertain whether the sugar-induced increase in SI mRNA level was caused by a direct contact of fructose to the absorptive cells or was indirectly mediated by alterations of certain humoral factors including insulin, which was recently reported to suppress the SI gene expression in the small-intestinal explants of adult rats.[17]

To examine whether the sugar-induced increases of SI gene expression occurs in the confined segments where fructose is in direct contact with the cells from the luminal side, we employed the jejunal perfusion technique. For this purpose, we developed a device that enabled us to simultaneously perfuse two different sugar solutions in the consecutive two jejunal segments. Compared with the adjacent segment obtained at the start of perfusion, SI mRNA level was elevated in the fructose-perfused segment, but not in the glucose-perfused segment. Because these two segments were not isolated from blood circulation, they were considered to be under the influence of similar levels of systemic hormones. Thus, this result strongly suggested that fructose

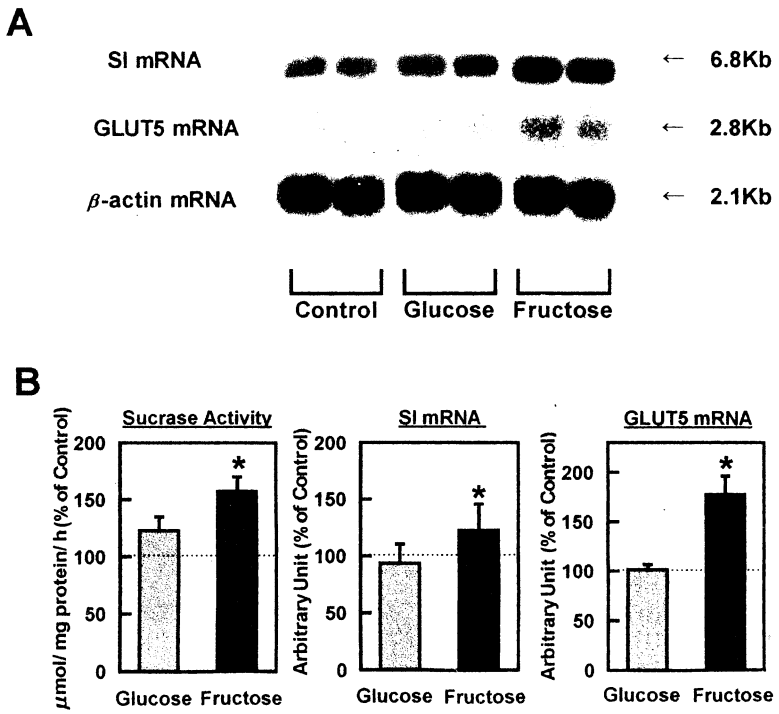


**Figure 3** Effects of short-term perfusion of glucose and fructose solutions on the sucrase activity and sucrase-isomaltase (SI) mRNA level in rat jejunum. Two adjacent 8-cm jejunal segments were simultaneously perfused with glucose and fructose solutions for 3 hours. A segment between the loops was obtained at the start of perfusion as a control segment. Representative Northern blots for SI mRNA, GLUT5 mRNA, and β-actin mRNA are shown in *Figure 3A*. The results for each sample normalized for the β-actin mRNA abundance were expressed as arbitrary units, representing the mean value of the control segment as 100% (*Figure 3B*). Sucrase activity is shown in relative activity representing the value in the adjacent control segment as 100%. Values represent means ± SEM for nine animals. Asterisks indicate significant differences compared with the glucose-perfused segment at $P < 0.05$ as assessed by paired *t*-test.

was capable of stimulating SI gene expression at the jejunal tissue where the absorption of this specific sugar took place. It should be noted that the short-term perfusion of the glucose solution resulted in an increase in sucrase activity without alterations in SI mRNA levels. This result may suggest that the posttranslational process or degradation of SI also is affected by certain sugars including glucose. Indeed, it was reported that dietary sucrose not only stimulated the synthesis of SI but also reduced the rate of degradation of SI in rat jejunum.[18]

SI is the only enzyme in the small intestine that can hydrolyze sucrose. Therefore, it seems reasonable that sucrose or its constituting monosaccharide should play a pivotal role in the regulation of SI gene expression. Sucrose is hydrolyzed to glucose and fructose, and these two monosaccharides are known to be subjected to carrier-mediated transfers through the brush-border membrane by sodium/D-glucose co-transporter (SGLT1)[19] and by a hexose transporter (GLUT5),[20,21] respectively. Miyamoto et al.[22] showed that feeding rats a diet rich in fructose caused a coordinate rise in the mRNA levels of intestinal hexose transporters including SGLT1 and GLUT5. We recently demonstrated that feeding a fructose diet to rats caused an enhancement of the transcription of GLUT5, as well as lactase-phlorizin hydrolase[23] and SI (Kishi et al., submitted). In this study, we found that fructose was able to enhance the mRNA levels of both SI and GLUT5 within a short period of time (3 hours). This result is consistent with recent reports that showed that dietary fructose caused a rapid increase in GLUT5 mRNA level in the jejunum of adult rats[24] and in weaning rats.[25] Recently, it also was reported in the human colon carcinoma cell line Caco-2 that the addition of fructose in the medium led to an elevation of GLUT5 mRNA level in as early as 8 hours.[26] Taken together, it is likely that fructose not only enhances the transcription of various genes related to intestinal carbohydrate digestion and absorption, but also induces its own transporter. This may result in a positive feedback of fructose transport and a pronounced effect of fructose on the gene expression of SI and GLUT5.

The molecular mechanisms whereby fructose enhances the expressions of SI and GLUT5 genes are uncertain at present. Mahraoui et al.[27] isolated the promotor region of the human GLUT5 gene and found that it contained two potential cyclic AMP (cAMP)-response elements (CRE). The extensive characterization of the promotor regions of human and mouse SI genes revealed several cis-acting elements essential for intestine-specific expression of the genes, which interact with respective nuclear proteins including Cdx2, HNF1α, and HNF1β.[28] However, it is not known whether the SI gene contains CRE. It should be worthwhile to investigate whether the known cis-acting elements in the promotor of the SI gene are involved in the fructose-induced increase in the gene expression of SI in the future studies.

Dietary carbohydrates including fructose are known to stimulate the gene expression of L-pyruvate kinase, a key enzyme for glycolytic pathway, at the transcription level in the liver, kidney, and small intestine.[29] In the 5′ flanking region of the L-pyruvate kinase gene, a regulatory cis element was found to respond to administration of fructose as well as glucose, leading to a designation of the element as "carbohydrate-response element."[30] In a study using transgenic mice containing the 5′ flanking region of the L-pyruvate kinase gene linked to the chloramphenicol acetyltransferase gene, Noguchi et al.[31] showed that dietary fructose enhanced the transcription of L-pyruvate kinase in the small intestine, whereas dietary glucose was unable to enhance L-pyruvate kinase gene expression in the small intestine. Therefore, it is likely that fructose may be metabolized faster than glucose in the small intestine. Hence, we

speculate that an intermediate metabolite produced in a glycolytic pathway may be involved in the regulation of the gene expressions of SI and GLUT5. From this aspect, it should be noted that the L-pyruvate kinase mRNA level in the cultured hepatocytes was reported to be related to the levels of 3-phosphoglycerate and phosphoenolpyruvate in the cells.[32] An alternative explanation for the minimal effect of glucose on the SI mRNA level may be that SI gene expression is rather repressed by high concentrations of glucose, as has been demonstrated in the Caco-2 cells.[33] These in vitro studies support the notion that the expression of the genes encoding the proteins participating in the digestion and absorption of carbohydrates in enterocytes are changeable by the luminally administered carbohydrates even in the absence of hormonal factors.

In conclusion, the present study demonstrated that both SI mRNA and GLUT5 mRNA levels were rapidly elevated by luminally administered fructose, but not by glucose. This result may suggest that fructose or its metabolites evoke an enhanced accumulation of SI mRNA and GLUT5 mRNA in the small intestine, presumably through a common regulatory mechanism. Further studies are required to elucidate the mechanism whereby fructose induces the gene expressions of SI and GLUT5 in the small intestine.

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