

L-Arabinose Selectively Inhibits Intestinal Sucrase in an Uncompetitive Manner and Suppresses Glycemic Response After Sucrose Ingestion in Animals

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The objective of this study was to investigate the effects of L-arabinose on intestinal α -glucosidase activities in vitro and to evaluate its effects on postprandial glycemic responses in vivo. L-Arabinose inhibited the sucrase activity of intestinal mucosa in an uncompetitive manner (K_i , 2 mmol/L). Neither the optical isomer D-arabinose nor the disaccharide L-arabinobiose inhibited sucrase activity, whereas D-xylose was as potent as L-arabinose in inhibiting this activity. L-Arabinose and D-xylose showed no inhibitory effect on the activities of intestinal maltase, isomaltase, trehalase, lactase, and glucoamylase, or pancreatic amylase. In contrast, a known α -glucosidase inhibitor, acarbose, competitively inhibited (K_i , 1.1 μ mol/L) sucrase activity and also inhibited intestinal maltase, glucoamylase, and pancreatic amylase. L-Arabinose suppressed the increase of blood glucose after sucrose loading dose-dependently in mice (ED_{50} , 35 mg/kg), but showed no effect after starch loading. The suppressive effect of D-xylose on the increase of blood glucose after sucrose loading was 2.4 times less than that of L-arabinose, probably due to intestinal absorption of the former. Acarbose strongly suppressed glycemic responses in both sucrose loading (ED_{50} , 1.1 mg/kg) and starch loading (ED_{50} , 1.7 mg/kg) in mice. L-Arabinose suppressed the increase of plasma glucose and insulin in rats after sucrose loading, the suppression of the former being uninterruptedly observed in mice for 3 weeks. Thus, the results demonstrated that L-arabinose selectively inhibits intestinal sucrase activity in an uncompetitive manner and suppresses the glycemic response after sucrose ingestion by inhibition of sucrase activity.

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IT HAS BEEN PROVEN that strict glycemic control is associated with a low incidence of microvascular and macrovascular complications in diabetes,¹ and a delay and/or inhibition of carbohydrate digestion could be helpful for avoiding postprandial hyperglycemia in diabetic patients.^{2,3} Specific inhibitors of α -glucosidases have shown a definite therapeutic value in suppressing the postprandial glycemic increase by delaying carbohydrate digestion.^{2,4} Acarbose²⁻⁶ and its analog⁷ are known to be competitive inhibitors of the intestinal α -glucosidases, ie, glucoamylase, sucrase, and maltase. It has also been shown that pancreatic amylase is inhibited by acarbose.⁶ Although the major portion of dietary carbohydrate is starch, daily ingestion of sucrose is large in many advanced countries (60 g/person · d, 1991, Japan); however, agents that selectively inhibit sucrose digestion have been of no practical use.

In our preliminary studies, we observed that the L-arabinose-containing fraction obtained by enzymatic hydrolysis of plant gums and sugar beet suppressed the increase of blood glucose after sucrose loading in mice. L-Arabinose is known as a less absorptive pentose with a sweet taste. Although broadly present in nature, it has been little used to date, and there are no known reports of its physiological effect in vivo.

The objective of this study was to investigate the effects of L-arabinose and related pentoses on the activities of intestinal α -glucosidases and pancreatic amylase in vitro, and to evaluate the effects of L-arabinose on postprandial glycemic responses using several experimental animals in vivo.

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MATERIALS AND METHODS

Inhibitory Effect on α -Glucosidase Activities of Porcine Intestinal Mucosa and on Amylase Activity of Mice Pancreas

Small intestines of pigs were obtained immediately after death at a slaughterhouse, rinsed with ice-cold saline, and stored at -20°C until use. The small intestines were thawed and cut open, and the mucosa was gently scraped off with a glass cover slip. All the collected mucosa from three pigs was homogenized together with 5 mmol/L EDTA-phosphate buffer (pH 7.0) and centrifuged at 4°C for 60 minutes at $60,000 \times g$, and the resulting pellet was collected and stored at -20°C until use. The pellet was rehomogenized with 10 mmol/L phosphate buffer (pH 7.0) and used for assay of the activities of sucrase, maltase, isomaltase, trehalase, lactase, and glucoamylase by the methods of Caspary and Graf⁵ and Dahlqvist.⁸ The standard assay mixture contained 150 μ L 100-mmol/L maleate buffer (pH 6.8), 25 μ L substrate solution (200 mmol/L sucrose, maltose, trehalose, and lactose, 100 mmol/L isomaltose, and 20 mg/mL soluble starch, for assay of sucrase, maltase, trehalase, lactase, isomaltase, and glucoamylase activity, respectively), and 50 μ L of a test substance solution (final concentration, 1 and 10 mmol/L for L-arabinose, D-arabinose, L-arabinobiose, D-xylose, L-xylose, and D-xylulose and 3 or 10 μ mol/L for acarbose). The reaction was initiated by addition of 25 μ L of appropriate dilutions of intestinal mucosa preparations (total assay vol, 250 μ L) and performed for 15 minutes at 37°C , and then the glucose concentration of the reaction mixture was determined. Specific activity was calculated as micromoles of substrate hydrolyzed per milligram protein within 1 minute. For amylase assay, pancreases were removed from five mice and homogenized together with 10 mmol/L phosphate buffer (pH 7.0), and the homogenate was used for amylase assay with the method of Whelan.⁹

Kinetic Analysis of Sucrase Inhibition by L-Arabinose

To learn the mode of the inhibitory effect of L-arabinose on intestinal sucrase activity, mucosal homogenate prepared from the porcine intestines mentioned earlier was incubated with increasing concentrations of sucrose in the absence and presence of two concentrations of L-arabinose (1 and 3 mmol/L) or acarbose (0.62 and 1.55 μ mol/L). Doses of L-arabinose were selected based on results of the inhibitory effect on sucrase activity by 1 and 10 mmol/L L-arabinose (first experiment). Doses of acarbose were

determined according to the results of Caspary and Graf.⁵ Results were plotted according to Lineweaver-Burk.

Effects of L-Arabinose, D-Xylose, and Acarbose on Blood Glucose Level After Sucrose or Starch Loading in Mice

To evaluate the potency of L-arabinose, D-xylose, and acarbose *in vivo*, the effects of these substances on plasma glucose after sucrose or starch loading were examined.

Five-week-old male ICR mice were purchased from Charles River Japan (Atsugi, Japan). Six mice in each group were fasted overnight for 16 hours before the experiment. L-Arabinose (0, 12.5, 25, and 50 mg/kg), D-xylose (0, 12.5, 25, and 50 mg/kg), or acarbose (0, 0.625, 1.25, and 2.5 mg/kg) was orally administered via gavage with 1 g/kg sucrose. In the preliminary study in mice, 25 mg/kg L-arabinose, 25 mg/kg D-xylose, and 1.25 mg/kg acarbose were found to be effective for suppression of the blood glucose increase after sucrose loading, and thus we selected three doses that covered 25 mg/kg L-arabinose and D-xylose and 1.25 mg/kg acarbose, respectively. In the starch loading test, L-arabinose (0, 25, 50, and 100 mg/kg) or acarbose (0, 0.625, 1.25, and 2.5 mg/kg) was orally administered via gavage with 1 g/kg soluble starch. At 0, 15, 30, 60, and 120 minutes after loading, 10 μ L blood was taken from the orbital sinus for glucose determination.

ED₅₀ values were obtained as follows. First, the mean increase in blood glucose at 15, 30, 60, and 120 minutes after loading versus the basal value was plotted, and the area under the curve of the blood glucose increase was calculated. Second, the inhibition ratio for each dose to the control group was calculated as follows: inhibition ratio (%) = $(1 - T/C) \times 100$, where T is the area of blood glucose increase during 120 minutes in the treated group, and C is the area of blood glucose increase during 120 minutes in the control group. The area of blood glucose increase during 120 minutes was calculated by the area surrounded by the glucose curve and the X-axis using the trapezoidal rule. Third, ED₅₀ and ED₂₀ values for acarbose, L-arabinose, and D-xylose were obtained by the corresponding dosage with 50% inhibition and 20% inhibition, respectively.

Effect of L-Arabinose on Plasma Glucose and Insulin Levels After Sucrose Loading in Rats

Rats were used in the experiment to evaluate the effects of L-arabinose on both plasma glucose and insulin. As in the previous experiments, 5-week-old male Wistar rats were purchased from Charles River Japan. The day before the experiment, a polyethylene catheter was inserted into the left jugular vein under ether anesthesia. The other end of the catheter was tunneled subcutaneously to exit the back of the neck. The catheter was filled with saline containing sodium heparin (200 U/mL) and plugged with stainless wire at the open end until the experiment. Rats were housed in individual cages after surgery. In the experiment, five rats in each group were fasted overnight for 16 hours. L-Arabinose (0, 50, and 100 mg/kg) was orally administered via gavage with 2.5 g/kg sucrose. L-Arabinose 50 mg/kg was found to be effective in suppressing the blood glucose increase after sucrose 2.5 g/kg had been administered to rats in the preliminary study; thus, we selected two doses including L-arabinose 50 mg/kg. At 0, 15, 30, 60, and 120 minutes after loading, 1 mL blood was taken from the catheter for determination of plasma glucose and insulin.

Influence of Consecutive Use of L-Arabinose on Glycemic Responses After Sucrose Loading in Mice

This experiment examined whether L-arabinose would be effective for plasma glucose if consecutively used. Eight-week-old male ICR mice were divided into two groups ($n = 6$): (1) control and (2)

L-arabinose-treated. Sucrose was administered orally to the control group via gavage once per day at a dose of 1 g/kg for 3 weeks. The L-arabinose-treated group was administered 25 mg/kg L-arabinose simultaneously with 1 g/kg sucrose once per day for 3 weeks. Once per week, mice were fasted overnight for 16 hours. After administration of 1 g/kg sucrose or 25 mg/kg L-arabinose with 1 g/kg sucrose, 10 μ L blood was taken from the orbital sinus at 0, 15, 30, 60, and 120 minutes to determine glucose levels. The area of the blood glucose increase during 120 minutes was calculated by the method described earlier.

Absorption of L-Arabinose in Rats

Five-week-old male Wistar rats were divided into seven groups ($n = 3$). Rats from six groups were orally administered via gavage a single dose of L-arabinose at 1,000 mg/kg. Blood samples were taken from each group by cardiac puncture at 0.5, 1, 2, 4, 8, and 24 hours, respectively, after the administration, and then plasma concentrations of L-arabinose were measured. L-Arabinose concentration in plasma from nontreated rats ($n = 3$) was designated as the basal value.

Urinary Excretion of L-Arabinose and D-Xylose in Rats

Five-week-old male Wistar rats were divided into three groups ($n = 6$) and orally administered L-arabinose (1,000 mg/kg) or D-xylose (1,000 mg/kg) via gavage. The control rats received water in the same manner. Immediately after administration, rats were housed individually in metabolic cages and allowed free access to tap water and diet. Urine flow during 0 to 24 hours was collected to determine L-arabinose and D-xylose concentrations. The urine of control rats was similarly collected for determination of basal excretion of L-arabinose and D-xylose.

Analytical Methods

Glucose was determined by the glucose oxidase method (Glucose-B Test; Wako Pure Chemical Industries, Osaka, Japan), and plasma insulin was measured by the enzyme immunoassay (EIA) method (Glazyme Insulin-EIA Test; Wako). Protein was determined by the method of Lowry et al.¹⁰ Plasma L-arabinose was determined enzymatically by the method of Sturgeon.¹¹ Urinary concentrations of L-arabinose and D-xylose were determined simultaneously by high-performance liquid chromatography (HPLC) under the following conditions: columns, Shodex Ionpack KS-801 (8 $\times$ 300 mm; Showa Denko, Tokyo, Japan) and Shodex Sugar SH-1011 (8 $\times$ 300 mm; Showa Denko); mobile phase, H₂O; flow rate, 1.0 mL/min; column temperature, 80°C; and refractive index by the detector.

Statistics

Data are expressed as the mean $\pm$ SEM. Comparisons were made using one-way ANOVA, with means testing by Dunnett's test when appropriate. *P* values less than .05 were considered significant. When the comparison was only between two groups, Student's *t* test was used.

RESULTS

Inhibitory Effect on α -Glucosidase Activities of Porcine Intestinal Mucosa and on Amylase Activity of Mice Pancreas

L-Arabinose (10 mmol/L) potentially inhibited sucrase activity but showed no inhibition of maltase, isomaltase, trehalase, lactase, or glucoamylase activities of porcine intestinal mucosa, and did not inhibit amylase activity of the mice pancreas homogenate (Table 1). However, acarbose 3

Table 1. Inhibitory Effect on α -Glucosidase Activities of Porcine Intestinal Mucosa and on Amylase Activity of Mice Pancreas

α -Glucosidase Activity	Acarbose		L-Arabinose		D-Xylose	
	Dose (μ mol/L)	Inhibition (%)	Dose (mmol/L)	Inhibition (%)	Dose (mmol/L)	Inhibition (%)
Porcine intestine						
Sucrase	3	97.3 $\pm$ 1.9	10	64.9 $\pm$ 0.8	10	57.6 $\pm$ 3.9
Maltase	3	88.9 $\pm$ 4.0	10	9.6 $\pm$ 1.2	10	12.0 $\pm$ 3.7
Isomaltase	10	11.2 $\pm$ 2.0	10	3.1 $\pm$ 1.8	10	3.1 $\pm$ 2.0
Trehalase	10	1.5 $\pm$ 2.2	10	0.3 $\pm$ 1.5	10	2.1 $\pm$ 0.8
Lactase	10	0.4 $\pm$ 1.6	10	-1.1 $\pm$ 2.3	10	-2.5 $\pm$ 4.1
Glucosylase	3	99.4 $\pm$ 0.6	10	0.4 $\pm$ 1.6	10	0.1 $\pm$ 0.5
Mouse pancreas						
Amylase	10	59.9 $\pm$ 5.8	10	-0.6 $\pm$ 1.6	10	1.6 $\pm$ 3.9

NOTE. Values are the mean $\pm$ SEM of 3 experiments.

μ mol/L inhibited the activities of sucrase, maltase, and glucoamylase of the intestinal mucosa, and also inhibited pancreatic amylase activity at a concentration of 10 μ mol/L. Some pentoses and L-arabinose-related disaccharide were examined for effects on the sucrase activity of porcine intestinal mucosa. Neither D-arabinose, an optical isomer of L-arabinose, nor L-arabinobiose, a disaccharide, inhibited this activity. Among the stereoisomers of L-arabinose, D-xylose was as potent as L-arabinose, whereas the optical isomer L-xylose had no inhibitory effect (Table 2).

Kinetic Analysis of Sucrase Inhibition by L-Arabinose

Lineweaver-Burk plots of the results revealed that L-arabinose inhibited sucrase activity in an uncompetitive manner, whereas acarbose inhibited it in a fully competitive manner (K_i , 2.0 mmol/L and 1.1 μ mol/L, respectively; Fig 1A and B). L-Arabinose had a 12.0-fold higher affinity for sucrase than for its natural substrate, sucrose.

Effects of L-Arabinose, D-Xylose, and Acarbose on Blood Glucose Levels After Sucrose or Starch Loading in Mice

L-Arabinose suppressed the increase of blood glucose dose-dependently after sucrose loading in fasted mice (Fig 2A), but showed no effect on this increase after starch loading (Fig 2B). Acarbose, in contrast, suppressed the increase of blood glucose in both sucrose and starch

Table 2. Inhibitory Effect of L-Arabinose and Related Sugars on Porcine Intestinal Sucrase Activity

Sugar	Dose (mmol/L)	Inhibitory Ratio (%)
L-Arabinose	1	12.9 $\pm$ 0.9
	10	56.2 $\pm$ 4.3
D-Arabinose	1	0.8 $\pm$ 0.3
	10	0.8 $\pm$ 0.4
L-Arabinobiose	1	0.7 $\pm$ 0.4
	10	0.3 $\pm$ 0.3
D-Xylose	1	14.3 $\pm$ 2.7
	10	52.1 $\pm$ 1.4
L-Xylose	1	0.3 $\pm$ 0.6
	10	0.6 $\pm$ 0.3
D-Xylulose	1	0.6 $\pm$ 0.3
	10	0.5 $\pm$ 0.8

NOTE. Values are the mean $\pm$ SEM of 3 to 5 experiments.

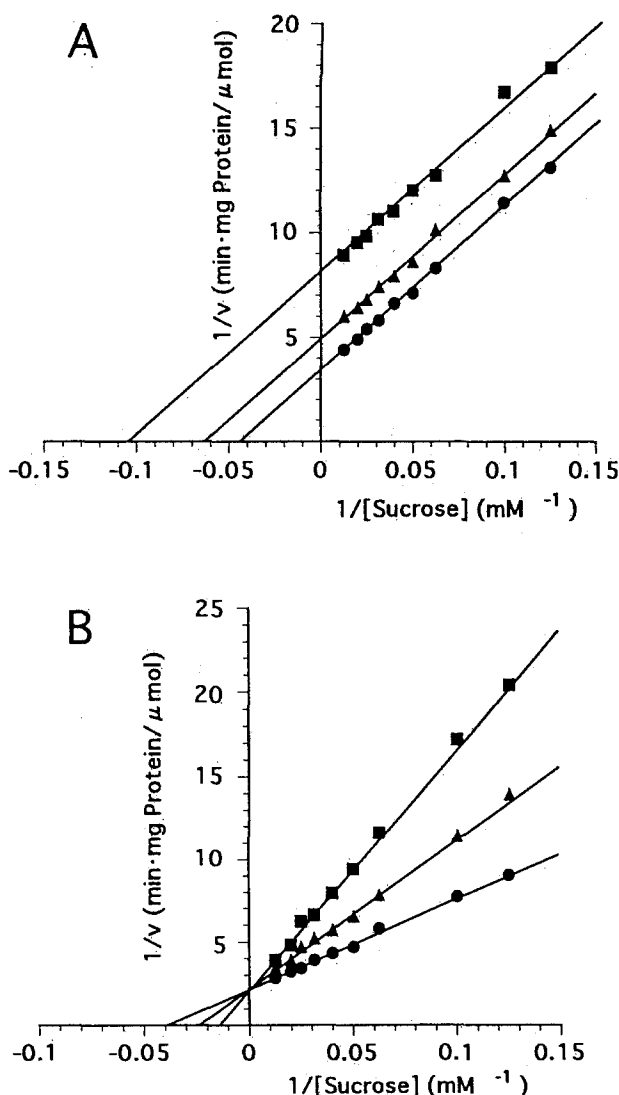


Fig 1. Kinetic analysis of sucrase inhibition by L-arabinose (A) and acarbose (B). Mucosal homogenates prepared from porcine intestine were incubated with increasing concentrations of sucrose in the absence and presence of inhibitor: (A) L-arabinose (Δ) 1 mmol/L or ($\blacksquare$) 3 mmol/L and (B) acarbose (Δ) 0.62 μ mol/L or ($\blacksquare$) 1.55 μ mol/L. ($\bullet$) Assays without inhibitor. Results are plotted according to Lineweaver-Burk.

loading. The ED_{50} value can be estimated as around 35 mg/kg for L-arabinose and 1.1 mg/kg for acarbose in the sucrose-loading test. ED_{20} value can be estimated to be around 44 mg/kg for D-xylose and 18.5 mg/kg for L-arabinose. The former value was 2.4 times less potent than the latter (Fig 2A).

Effect of L-Arabinose on Plasma Glucose and Insulin Levels After Sucrose Loading in Rats

Basal values for plasma glucose and insulin in fasted rats were 76.2 ± 4.82 mg/dL and 2.2 ± 0.87 μ U/ml, respectively. L-Arabinose (50 and 100 mg/kg) significantly suppressed the increase of plasma glucose levels after sucrose loading in fasted rats (Fig 3A): 15 minutes after ingestion, the increase was suppressed approximately 50% by both 50 mg/kg and 100 mg/kg L-arabinose. Significant suppression lasted from 15 to 60 minutes in the L-arabinose (100 mg/kg) group. L-Arabinose also significantly suppressed the increase in plasma insulin after sucrose loading (Fig 3B): 15 minutes after ingestion, the increase was suppressed 57% and 64% by 50 mg/kg and 100 mg/kg L-arabinose, respectively.

Influence of Consecutive Use of L-Arabinose on Glycemic Responses After Sucrose Loading in Mice

In the control group, the area of the blood glucose increase after sucrose loading significantly increased 2 and 3 weeks later (Fig 4); in the L-arabinose-treated group, the area of the glucose increase was significantly suppressed on the first day of the experiment. The area of the glucose increase in the L-arabinose-treated group also significantly increased after consecutive sucrose feeding; however, the suppression ratio was almost constant (28.3% ~ 32.2%).

Absorption of L-Arabinose in Rats

The basal concentration of L-arabinose in rat plasma was 5.4 ± 1.37 μ g/mL. In this study, L-arabinose was determined enzymatically using galactose dehydrogenase (EC 1.1.1.48). Galactose dehydrogenase catalyzes the following two reactions: (1) L-arabinose + NAD $\rightarrow$ L-arabinonic

acid + NADH + H^+ ; and (2) D-galactose + NAD $\rightarrow$ D-galactonic acid + NADH + H^+ . The basal value of 5.4 μ g/mL is thus virtually the sum of the concentrations of L-arabinose and D-galactose in rat plasma. After oral administration of L-arabinose, plasma concentrations of L-arabinose were low, and 38.6 ± 2.0 μ g/mL at 30 minutes was the highest value (Fig 5).

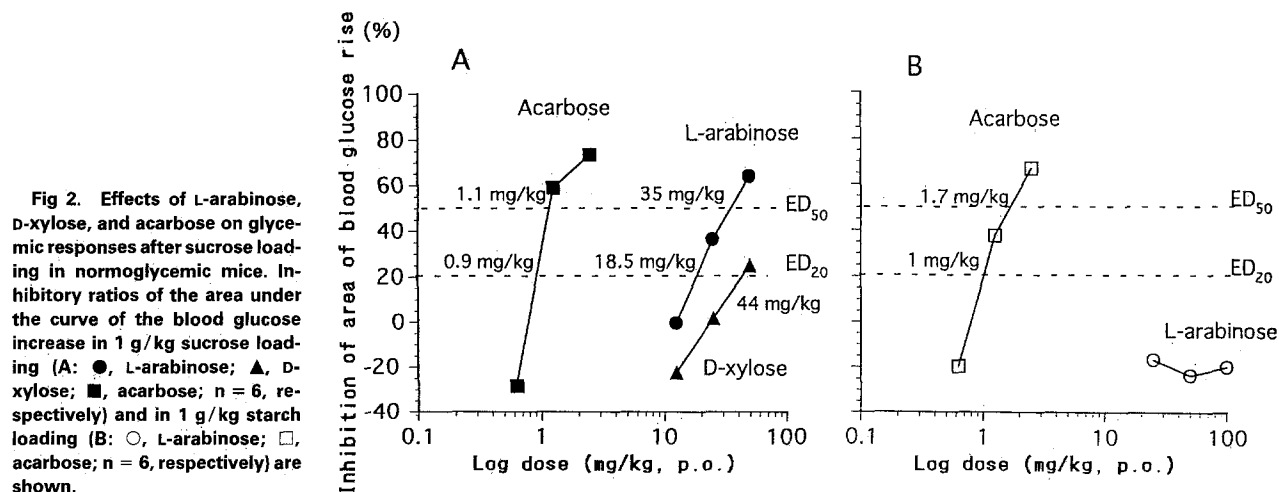
Urinary Excretion of L-Arabinose and D-Xylose in Rats

There was a significant difference between L-arabinose-treated and D-xylose-treated ingested rats for the ratio of urinary excretion to ingested dose (L-arabinose, $3.5\% \pm 0.13\%$; D-xylose, $22.8\% \pm 0.63\%$; Fig 6). This result suggested that L-arabinose is a much less absorbable pentose than D-xylose.

DISCUSSION

We demonstrated in this study that L-arabinose selectively inhibited the sucrase activity of porcine intestinal mucosa in an uncompetitive manner. We also showed that L-arabinose suppressed the increase of blood glucose dose-dependently after ingestion of sucrose but did not suppress this increase after starch ingestion in mice. L-Arabinose also suppressed the increase of plasma glucose and insulin after sucrose ingestion in rats. Semenza and Balthazar¹² reported a similar inhibition of sucrase activity by L-arabinose in rabbit in vitro; however, they did not examine the selectivity. In addition, no known in vivo studies have been reported until this one.

Acarbose and other α -glucosidase inhibitors^{2-7,13,14} are recognized as potent competitive inhibitors of the activities of intestinal glucoamylase, maltase, and sucrase, and it has also been shown that acarbose has an inhibitory effect on pancreatic amylase activity.⁶ We confirmed these results in this study. In many advanced countries, starch accounts for approximately 60%, sucrose 30%, and lactose 10% of ingested carbohydrates.⁵ Since the digestion of both starch and sucrose is delayed by acarbose and its analogs, these α -glucosidase inhibitors have a valuable therapeutic effect



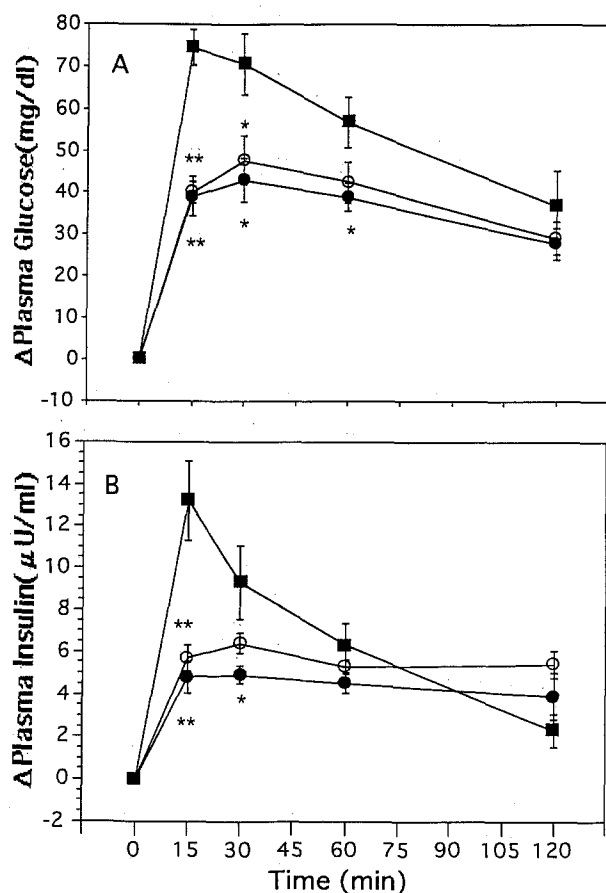


Fig 3. Effects of L-arabinose on plasma glucose (A) and insulin (B) after sucrose loading in rats. Overnight-fasted Wistar rats were given 2.5 g/kg sucrose (■), and blood samples were taken at 0, 15, 30, 60, and 120 minutes after the loading to determine plasma glucose and insulin. L-Arabinose (○, 50 mg/kg; ●, 100 mg/kg) was administered simultaneously with sucrose. Values are the mean ($n = 5$) $\pm$ SEM. ** $P < .01$, * $P < .05$: L-arabinose-treated group *v* control group.

in reducing postprandial hyperglycemia in diabetic patients.^{2,3}

The major portion of dietary carbohydrate is starch, but sucrose is used in many foods as a sweetener or other ingredient, and its daily intake is large in many advanced countries. It has been shown that Tris competitively inhibits intestinal sucrase and suppresses the increase in blood glucose after sucrose ingestion by rats and human subjects¹⁵; however, Tris is of no practical use, because of its unpleasant taste and the necessity of large doses. Thus, there are no known inhibitors of practical use that selectively inhibit intestinal sucrase and delay the ingestion of sucrose.

L-Arabinose is a natural pentose with a sweet taste. In this study, it suppressed the increase in blood glucose at a low dose after sucrose ingestion (ED_{50} , 35 mg/kg) but showed no suppression of the increase in blood glucose after starch loading in mice. Furthermore, in our preliminary study, we found that approximately 25 to 100 mg/kg L-Arabinose showed no effect on the blood glucose increase in a glucose loading test (1 g/kg) in mice and that there was no delay of the peak, in contrast to the effects of guar gum

in the same test, which suppressed the blood glucose increase and delayed the peak. These results suggest that L-arabinose does not affect the glucose absorption or gastric emptying. Among the pentoses structurally related to L-arabinose, D-xylose was equally potent in its inhibitory effect on the sucrase activity of porcine intestinal mucosa in this study. Neither D-arabinose nor L-xylose inhibited sucrase activity, nor did L-arabinobiose, a dimer of L-arabinose. These results suggest that some stereospecific interaction may exist among the intestinal sucraes, the inhibitory pentoses, and the substrate to elicit the inhibitory action of L-arabinose or D-xylose.

Although D-xylose was as potent as L-arabinose in its inhibitory effect on sucrase activity *in vitro*, its potency for suppression of the blood glucose increase following sucrose ingestion was 2.4 times lower. The difference in potency between the two substances *in vivo* might depend on the difference in their absorption ratio after oral administration from the small intestine. To explore this possibility, we compared the urinary excretion rates after oral administration, and found that the excretion ratio of D-xylose was 6.5 times greater than that of L-arabinose. Thus, we can conclude that L-arabinose is less absorbable than D-xylose, and an effective L-arabinose concentration in the small intestine can be maintained while the concentration of D-xylose in the small intestine may rapidly decrease, resulting in a weaker *in vivo* effect of D-xylose. A similar difference in the absorption between D-xylose and L-arabinose has been demonstrated in other species.¹⁶⁻¹⁸ Another interesting biological difference between them was reported by Segal and Foley,¹⁹ who demonstrated that D-xylose was catabolized to respiratory $^{14}CO_2$ to some extent but that L-arabinose gave rise to negligible amounts of respiratory $^{14}CO_2$ in a study of the metabolic fate of injected ^{14}C -labeled pentoses in man. These findings sug-

(mg/dl $\cdot$ 2h)

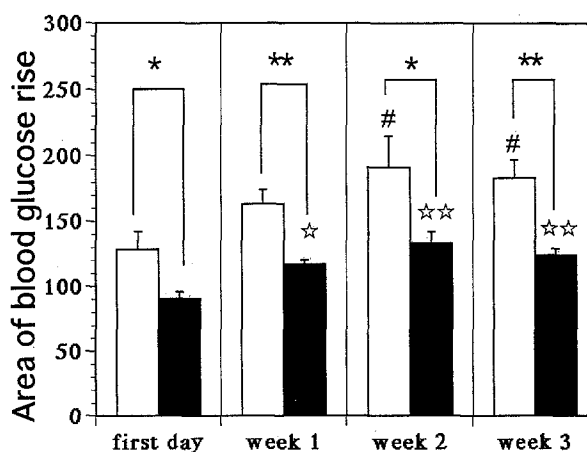


Fig 4. Influence of consecutive ingestion of sucrose on the glyce-mic response after sucrose loading and the effect of L-arabinose in mice. Values are the mean $\pm$ SEM ($n = 6$) for the area of the blood glucose increase in controls (□) and L-arabinose-treated rats (■). ** $P < .01$, * $P < .05$: L-arabinose-treated group *v* control group. # $P < .05$ *v* first day in control group. ☆☆ $P < .01$, ☆ $P < .05$: *v* first day in L-arabinose-treated group.

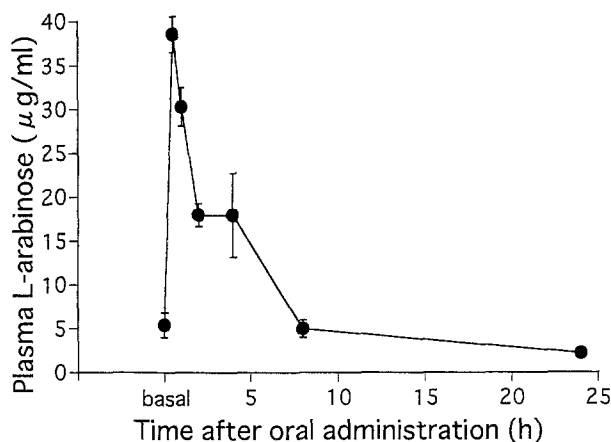


Fig 5. Plasma concentration of L-arabinose after oral administration in rats. L-Arabinose concentration in plasma from a nontreated group of animals ($n = 3$) is shown as the basal value. Values are the mean $\pm$ SEM.

gest that a larger quantity of D-xylose, greater than 22.8%, was excreted in the urine which had been absorbed from the intestine. The concept of good absorbability of D-xylose is consistent with the results of previous reports in which D-xylose was absorbed by an active transport process at low concentration.^{20,21}

Although the *in vitro* inhibitory potency of L-arabinose (K_i , 2.0 mmol/L) was low compared with acarbose (K_i , 1.1 μ mol/L), we found that L-arabinose possessed a more potent *in vivo* effect: the ED_{50} value of L-arabinose and acarbose was 35 and 1.1 mg/kg, respectively, in the sucrose loading test. One possible reason that the *in vivo* effect of L-arabinose is more potent than expected from *in vitro* experiments is its biochemical stability in the gastrointestinal tract and uncompetitive manner of sucrase inhibition, in addition to its low absorbability in the small intestine.

Consecutive sucrose feeding caused a significant increase of the areas under the curve of blood glucose. This might be due to an increase of intestinal sucrase activity, as reported in the sucrose-fed rat.^{22,23} Despite the increase in the area under the blood glucose curve after consecutive sucrose feeding, L-arabinose in the present study showed a stable, significant suppression of the glucose areas for 3 weeks, probably by inhibiting sucrase activity in the small intestine.

L-Arabinose is prevalent in nature as a component of plant gums and sugar beet. It has a potent, sweet taste and low toxicity; the LD_{50} value was approximately 20 g/kg orally in mice in our preliminary test. L-Arabinose caused no diarrhea at a dose of 1 g/kg in the rat study, nor was diarrhea observed in a human study in which eight healthy volunteers ingested 2 g L-arabinose with 50 g sucrose (Yao T, et al, unpublished data, October 1993). Although a definite therapeutic value of acarbose and other known α -glucosidase inhibitors in diabetic patients has been demonstrated, unpleasant side effects associated with incomplete absorption of dietary carbohydrate, ie, flatulence, abdominal discomfort, diarrhea,^{2,3} and ileus-like symptoms,²⁴ have been reported. These side effects may be due to the potent inhibition of amylase, maltase, and sucrase,

which in turn inhibits the digestion of both sucrose and starch. As shown in this study, L-arabinose only inhibited intestinal sucrase activity and specifically suppressed the blood glucose increase after sucrose ingestion, resulting in little adverse effect on the gastrointestinal tract.

There are three types of reversible enzyme inhibition: (1) competitive, (2) uncompetitive, and (3) noncompetitive. Our kinetic study of sucrase inhibition demonstrated that this was induced by L-arabinose in an uncompetitive manner and by acarbose in a competitive manner. A competitive manner is defined as one in which an inhibitor binds to the catalytic site of the enzyme and competes with the primary substrate, so that the activity of the enzyme is inhibited. An uncompetitive inhibition is defined as one in which an inhibitor binds only to an enzyme-substrate complex and inhibits its activity. An inhibition other than these two is defined as noncompetitive. Acarbose, a widely investigated α -glucosidase inhibitor, has been reported to be a competitive inhibitor of intestinal maltase, glucoamylase, and sucrase. We confirmed in this study that acarbose inhibited sucrase in a competitive manner, and found that L-arabinose selectively inhibited sucrase activity in an uncompetitive manner. Based on the results, we speculate that L-arabinose possesses a selective high affinity for intestinal sucrase-sucrose complex and forms a triple complex with a low sucrase activity, resulting in inhibition of sucrase.

In summary, the present study demonstrated that L-arabinose selectively inhibits intestinal sucrase activity in an uncompetitive manner and suppresses the plasma glucose increase after sucrose ingestion. Thus, L-arabinose may be useful in preventing postprandial hyperglycemia in diabetic patients when foods containing sucrose are ingested. This is the first report indicating selective inhibition of sucrase activity by L-arabinose both *in vitro* and *in vivo*.

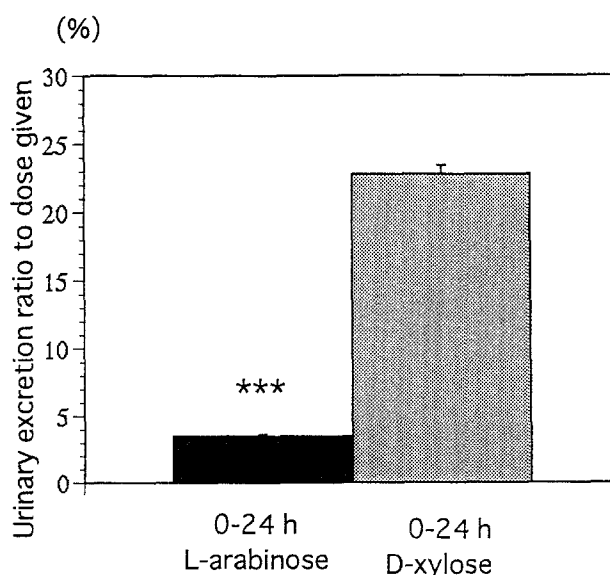


Fig 6. Urinary excretion of L-arabinose and D-xylose in rats. Values are the mean $\pm$ SEM. *** $P < .001$: L-arabinose group v D-xylose group.

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