Xylitol-Induced Increase in the Plasma Concentration and Urinary Excretion of Uridine and Purine Bases

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To determine whether xylitol increases the plasma concentration and urinary excretion of uridine together with purine bases, we administered xylitol (0.6 g/kg weight) intravenously to six normal subjects using a 10% xylitol solution. Xylitol infusion increased the plasma concentration and urinary excretion of uridine, as well as purine bases, while it decreased both the concentrations of inorganic phosphate in plasma and pyruvic acid in blood and increased the blood concentration of lactic acid. These results suggest that an increase in the plasma concentration and urinary excretion of uridine is ascribable to increased pyrimidine degradation following purine degradation induced by xylitol.

PREVIOUS STUDIES[1-3] have demonstrated that ischemia enhances both pyrimidine and purine degradation, resulting in an increase in the plasma concentration of uridine and purine bases. The ischemia-induced acceleration of pyrimidine degradation occurs concomitantly with that of purine degradation. Namely, ischemia disturbs aerobic glycolysis, leading to a decreased adenosine triphosphate (ATP) concentration and increased adenosine diphosphate (ADP) and monophosphate (AMP) concentrations. These changes enhance purine degradation (AMP → inosine monophosphate [IMP] → inosine → hypoxanthine → xanthine → uric acid). In addition, since uridine triphosphate (UTP) is produced by phosphorylation of uridine diphosphate (UDP) using ATP, a decrease in the ATP concentration results in decreased phosphorylation of UDP to UTP, leading to increased UDP and uridine monophosphate (UMP). These changes also enhance pyrimidine degradation (UTP → UDP → UMP → uridine), resulting in an increase in the plasma concentration of uridine (Fig 1). Therefore, these previous studies[1-3] seem to indicate that the abrupt consumption of ATP by any substance enhances pyrimidine degradation, as well as purine degradation.

Xylitol (a pentose alcohol) has been used as a supplement to meet energy needs in patients with diabetes mellitus, since it is used without the action of insulin in the body.[4-6] In previous studies,[7-9] it has been demonstrated that xylitol abruptly decreases ATP and increases ADP and AMP concentrations, enhancing purine degradation (Fig 2). Accordingly, it is suggested that xylitol enhances pyrimidine degradation, leading to the increased plasma concentration of uridine, as well as purine degradation, leading to the increased plasma concentration of purine bases. Therefore, to examine whether xylitol increases the plasma concentration of uridine and of purine bases, we administered xylitol intravenously to six healthy subjects.

SUBJECTS AND METHODS

Subjects and Protocol

The study was conducted on six healthy men aged 33 to 48 years and weighing 48 to 60 kg. The subjects had normal laboratory data. After informed consent was obtained, xylitol (0.6 g/kg weight) was infused over 1 hour as a 10% solution after an overnight fast except for water. Urine was completely voided 1 hour before beginning the xylitol infusion, and then urine was collected at an interval of 1 hour two times. Blood samples were drawn with heparinized syringes 30 minutes before beginning the xylitol infusion and then again 30 minutes and 1 hour after beginning the infusion. Two weeks later, the control study was also conducted on the same subjects. The protocol was the same as in the study just described, except physiological saline was used instead of 10% xylitol solution.

Blood and Urine Analyses

Plasma and urinary concentrations of hypoxanthine, xanthine, and uridine were determined by the method of Yamamoto et al[10] using high-performance liquid chromatography. The column used was a Wakosil 5C-18 (4.6 mm ID × 250 mm; Wako Pure Chemical Industries). The uric acid level in plasma and urine was measured by the uricase method using an autoanalyzer. Since it is necessary to prevent changes in the concentration of lactic acid and pyruvic acid by glycolysis in blood cells, blood samples were immediately treated without separation of the blood into blood cells and plasma, and blood concentrations of lactic acid and pyruvic acid were measured by enzymatic methods using a Determinar LA kit (Kiyowa Medix, Tokyo, Japan) and a Determinar PA kit (Kiyowa Medix), respectively. The plasma concentration of xylitol was determined by an enzymatic method described previously.[7]

Chemicals

Hypoxanthine, xanthine, and uridine were purchased from Wako Pure Chemical Industries (Osaka, Japan), and 10% xylitol solution was obtained from Otsuka Pharmaceuticals (Tokyo, Japan). Other chemicals were obtained from Wako Pure Chemical Industries.

Statistics

Values are expressed as the mean ± SD. The significance of differences was assessed by the two-tailed Student's *t* test for all variables. A P value less than .05 was considered statistically significant.

RESULTS

Plasma Concentrations of Xylitol

Plasma concentrations of xylitol were negligible, 65.4 ± 5.3 mg/dL, and 67.2 ± 9.6 mg/dL 30 minutes before, 30 minutes after, and 1 hour after beginning the xylitol infusion, respectively.

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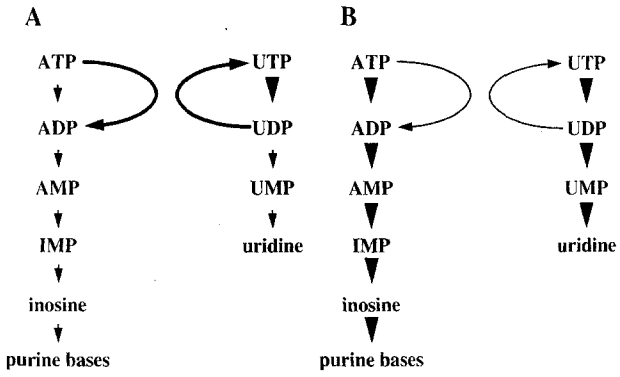

Fig 1. Schematic of pyrimidine and purine degradation induced by xylitol. (A) Before administration of xylitol; (B) during administration of xylitol. Thick arrows denote increased degradation.

Effect of Xylitol on Plasma Concentrations of Uridine, Hypoxanthine, Xanthine, and Uric Acid

Xylitol increased the plasma concentration of hypoxanthine 3.1-fold ($P < .05$), xanthine 2.6-fold ($P < .05$), uric acid 1.1-fold ($P < .01$), and uridine 1.5-fold ($P < .01$) 30 minutes after beginning the xylitol infusion, and it also increased plasma concentrations of hypoxanthine, xanthine, uric acid, and uridine 2.0-fold ($P < .01$), 2.6-fold ($P < .01$), 1.2-fold ($P < .05$), and 1.9-fold ($P < .01$), respectively, 1 hour after beginning the xylitol infusion as compared with the respective values 30 minutes before xylitol infusion (Table 1).In contrast, infusion of physiological saline did not affect plasma concentrations of hypoxanthine, xanthine, uric acid, or uridine (Table 1).

Effect of Xylitol on Urinary Excretion of Uridine, Hypoxanthine, Xanthine, and Uric Acid

Xylitol increased the 1-hour urinary excretion of hypoxanthine, xanthine, and uric acid 4.9-fold ($P < .01$), 2.9-fold ($P < .01$), and 1.4-fold ($P < .05$), respectively, as compared with the respective values before xylitol infusion (Table 2). Urinary excretion of uridine was negligible during 1 hour before xylitol infusion, whereas it was 3.22 ± 2.07 μmol/h during 1 hour after beginning the xylitol infusion (Table 2). However, physiological saline did not affect urinary excretion of hypoxanthine, xanthine, uric acid, or uridine.

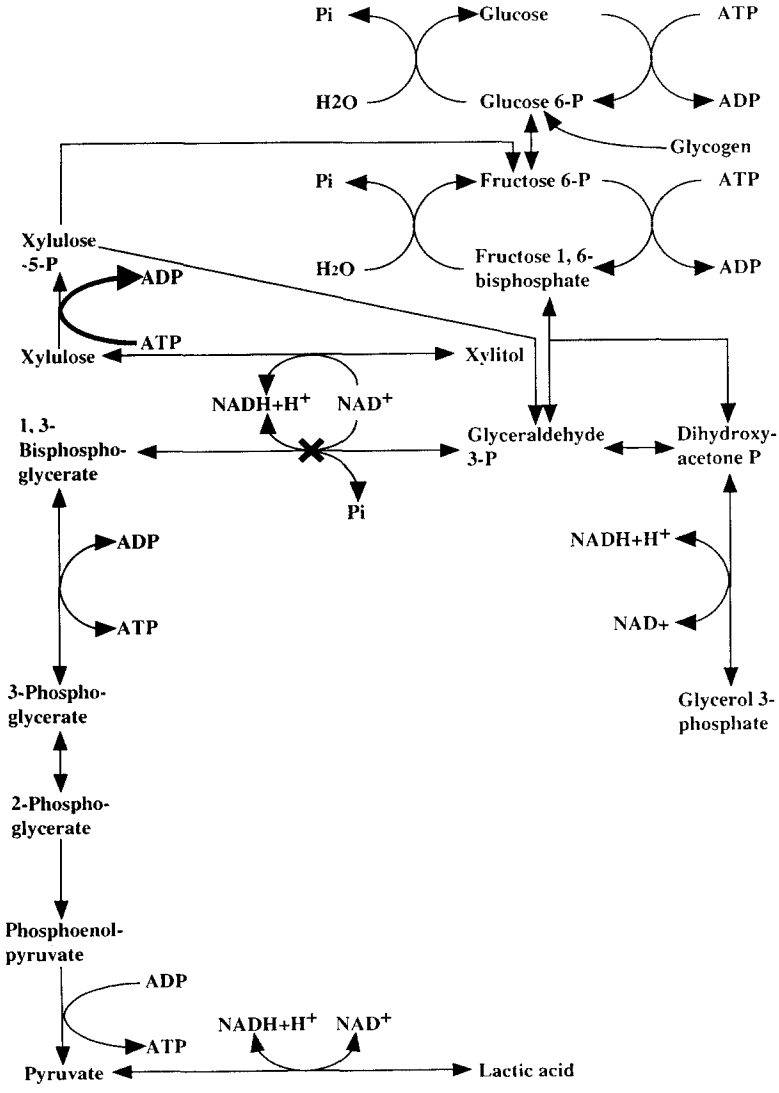

Fig 2. Consumption of ATP and inhibition of glycolysis by xylitol metabolism. X denotes the site of glycolysis inhibition; thick arrow denotes ATP consumption.

Table 1. Plasma Concentration of Hypoxanthine, Xanthine, Uric Acid, and Uridine (N = 6)

Condition	Period 1	Period 2	Period 3
Xylitol infusion			
Hypoxanthine	1.05 ± 0.12	3.25 ± 1.43*	2.13 ± 0.41†
Xanthine	0.73 ± 0.16	1.91 ± 0.63*	1.91 ± 0.30†
Uric acid	351 ± 44	396 ± 30†	417 ± 36*
Uridine	4.79 ± 0.63	7.03 ± 0.83†	9.26 ± 1.26†
Physiological saline infusion			
Hypoxanthine	1.02 ± 0.15	1.02 ± 0.14	0.99 ± 0.11
Xanthine	0.66 ± 0.11	0.66 ± 0.11	0.65 ± 0.11
Uric acid	347 ± 38	348 ± 40	345 ± 39
Uridine	4.63 ± 0.6	4.64 ± 0.57	4.66 ± 0.62

NOTE. Values are the mean ± SD (μmol/L). Period 1, 30 minutes before beginning xylitol infusion; 2, 30 minutes after beginning xylitol infusion; 3, 1 hour after beginning xylitol infusion.

*$P < .05$, †$P < .01$: *v* respective values at 1.

Relationship of an Increase in the Plasma Concentration of Purine Bases (hypoxanthine + xanthine + uric acid) and of Uric Acid With Increased Plasma Uridine

The xylitol-induced increase in the plasma concentration of purine bases correlated well with that of uridine, using all respective values 30 minutes and 1 hour after beginning the xylitol infusion ($r = .71$, $P < .01$; Fig 3), and the xylitol-induced increase in the plasma concentration of uric acid also correlated well with that of uridine ($r = .71$, $P < .01$; Fig 4).

Blood Concentrations of Inorganic Phosphate, Lactic Acid, and Pyruvic Acid

Xylitol decreased the plasma concentration of inorganic phosphate 0.84-fold ($P < .01$) and 0.75-fold ($P < .01$), respectively, 30 minutes and 1 hour after beginning the xylitol infusion, as compared with the preinfusion values (Table 3). Xylitol increased the blood concentration of lactic acid 1.53-fold ($P < .01$) and 1.81-fold ($P < .01$) 30 minutes and 1 hour after beginning the xylitol infusion, respectively, whereas it

Table 2. Urinary Excretion of Purine Bases and Uridine (N = 6)

Condition	Period 1	Period 2
Xylitol infusion		
Hypoxanthine	4.18 ± 0.65	20.60 ± 12.00†
Xanthine	3.02 ± 0.51	8.82 ± 3.18†
Uric acid	179 ± 27	254 ± 61*
Uridine	ND	3.22 ± 2.07*
Physiological saline infusion		
Hypoxanthine	4.21 ± 0.55	4.11 ± 0.70
Xanthine	3.34 ± 0.36	3.28 ± 0.49
Uric acid	172 ± 26	165 ± 25
Uridine	ND	ND

NOTE. Values are the mean ± SD (μmol/h). Period 1, 1 hour period before beginning xylitol infusion; 2, 1-hour period after beginning xylitol infusion.

Abbreviation: ND, not detected.

*$P < .05$, †$P < .01$: *v* respective values at 1.

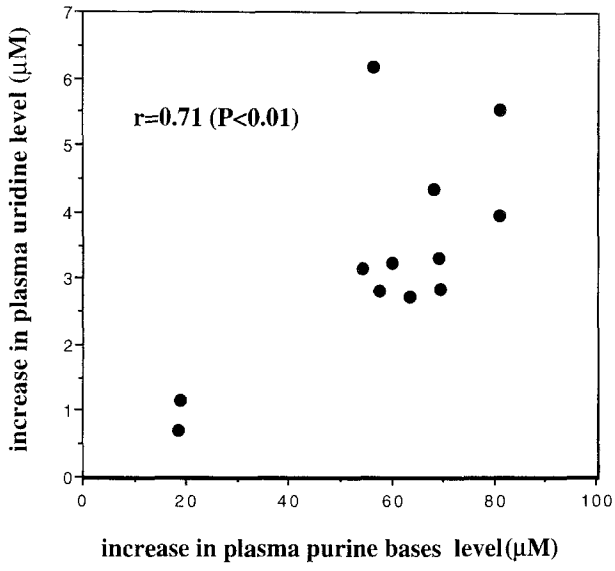

Fig 3. Relationship between plasma uridine increase and purine base increase.

decreased the blood concentration of pyruvic acid 0.69-fold ($P < .05$) 30 minutes after and 0.68-fold ($P < .05$) 1 hour after beginning the xylitol infusion. In the control study, physiological saline did not affect urinary excretion of hypoxanthine, xanthine, uric acid, or uridine.

DISCUSSION

Many previous studies[7-9] have demonstrated that xylitol abruptly consumes ATP during its metabolism and disturbs glycolysis (Fig 2). Namely, xylitol is metabolized to xylulose, which is then phosphorylated to xylulose-5-phosphate using ATP as a phosphate donor. ATP is consequently consumed, and both ADP and AMP increase together with other phosphory-

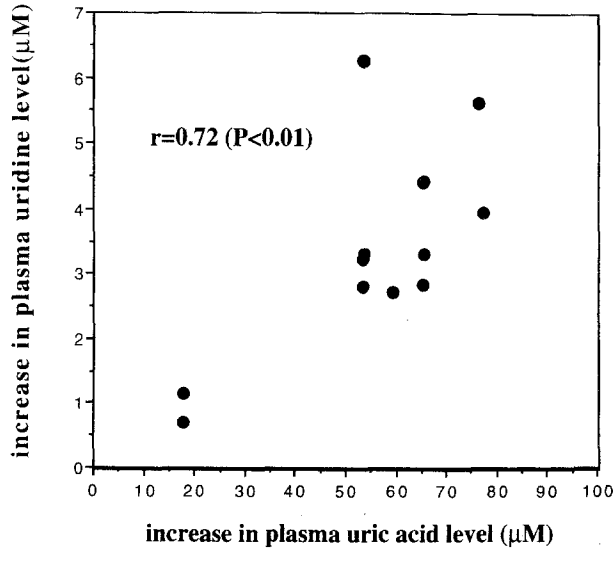

Fig 4. Relationship between plasma uridine increase and uric acid increase.

Table 3. Concentration of Inorganic Phosphate in Plasma and Lactic Acid and Pyruvic Acid in Blood (N = 6)

Condition	Period 1	Period 2	Period 3
Xylitol infusion			
Inorganic phosphate	1.07 ± 0.56	0.90 ± 0.46†	0.81 ± 0.10†
Lactic acid	0.69 ± 0.22	1.05 ± 0.32†	1.24 ± 0.22†
Pyruvic acid	57.2 ± 14.4	39.4 ± 6.2*	38.8 ± 4.0*
Physiological saline infusion			
Inorganic phosphate	1.06 ± 0.06	1.06 ± 0.06	1.06 ± 0.06
Lactic acid	0.72 ± 0.20	0.70 ± 0.15	0.69 ± 0.18
Pyruvic acid	54.4 ± 9.1	53.9 ± 10.0	54.5 ± 10.2

NOTE. Periods and statistical symbols are the same as in Table 1. Values are the mean ± SD (mmol/L for inorganic phosphate and lactic acid and μmol/L for pyruvic acid).

lated metabolites of xylitol. In addition, since xylitol is metabolized to D-xylulose, coupled with a reduction of NAD to NADH, the concentration of NAD decreases and that of NADH increases as shown by the xylitol-induced increase in the ratio of lactic acid to pyruvic acid in the blood (Table 3), which reflects a xylitol-induced increase in the NADH/NAD ratio in the cytosol. A decrease in the concentration of NAD disturbs glycolysis at the level of conversion of glyceraldehyde-3-phosphate to 1,3-bisphosphoglycerate, since the reaction is coupled with a reduction of NAD. The disturbance of glycolysis inhibits ATP production from ADP and increases phosphorylated glycolytic intermediates, including glyceraldehyde-3-phosphate and dihydroxyacetonephosphate. These increased phosphorylated metabolites trap inorganic phosphate, resulting in a decreased plasma concentration of inorganic phosphate (Table 3). Accordingly, a xylitol-induced increase in AMP and decrease in ATP and inorganic phosphate accelerates purine degradation from AMP to uric acid via IMP, inosine, hypoxanthine, and xanthine. In the present study, a xylitol-induced increase in the plasma concentration and urinary excretion of uric acid indicated that xylitol enhanced purine degradation as described previously.[7-9]

If it is correct that ATP consumption enhances pyrimidine degradation, xylitol increases both pyrimidine degradation and purine degradation, resulting in an increase in the plasma concentration and urinary excretion of uridine and purine bases. Therefore, to investigate whether xylitol induces pyrimidine degradation together with purine degradation, we measured the plasma concentration and urinary excretion of uridine before and during xylitol infusion. In addition, using plasma purine bases as a marker of purine degradation, we compared its increase by xylitol with the plasma uridine increase by xylitol to investigate whether an increase in the plasma concentration of uridine correlates with that of purine bases (a marker of purine degradation). This was because the increase in the blood concentration of lactic acid by xylitol infusion in the present study was not large enough to inhibit urinary excretion of uric acid, although a xylitol-induced increase in the blood concentration of lactic acid may partly play a role in an increase in the plasma concentration of uric acid, since lactic acid inhibits urinary excretion of uric acid but not of oxypurines.[11]

The present study demonstrated xylitol-induced increases in the plasma concentration and urinary excretion of uridine and purine bases, indicating that xylitol accelerated pyrimidine degradation, as well as purine degradation. Furthermore, a positive relationship was demonstrated between an increase in the plasma concentration of uridine and of purine bases (Fig 2) and between an increase in the plasma concentration of uridine and of uric acid, suggesting that increased pyrimidine degradation was associated with increased purine degradation during xylitol infusion. Therefore, it is suggested that the mechanism of the xylitol-induced pyrimidine degradation is similar to or the same as that of the ischemia-induced pyrimidine degradation, and also that abrupt consumption of ATP by any substance accelerates increased pyrimidine degradation, leading to the increased plasma concentration of uridine (Fig 1). In fact, besides xylitol, we recently demonstrated that pyrimidine degradation was accelerated by ethanol,[12] fructose,[12] and exercise,[13] which are well known to consume ATP abruptly and thereby increase purine degradation. An increase in the plasma concentration of oxypurines induced by fructose or ischemia is an indicator of purine degradation. However, an increase in the plasma concentration of oxypurines induced by xylitol or ethanol is attributable to both the enhancement of purine degradation and the inhibition of xanthine dehydrogenase activity by xylitol[8] or ethanol,[14] respectively. Therefore, an increase in the plasma concentration of oxypurines by xylitol or ethanol may not be an accurate indicator of purine degradation. In contrast, an increase in the plasma concentration of purine bases is an accurate indicator whatever the substance that induces the purine degradation, although the xylitol-induced increase in the plasma concentration of purine bases was most likely entirely due to those of uric acid (Table 1 and Figs 3 and 4). Furthermore, an increase in the plasma concentration of uridine induced by xylitol may be an accurate indicator of purine degradation, as well as pyrimidine degradation, since the plasma concentration of uridine is not affected by inhibition of xanthine dehydrogenase. Accordingly, an increase in the plasma concentration of uridine seems to be a better indicator of the purine degradation induced by xylitol than that of oxypurines.

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