Effect of Glucagon on the Xylitol-Induced Increase in the Plasma Concentration and Urinary Excretion of Purine Bases

Tetsuya Yamamoto, Yuji Moriwaki, Sumio Takahashi, Hiroyuki Ohata, Takashi Nakano, Jun-ichi Yamakita, and Kazuya Higashino

To investigate whether glucagon affects the xylitol-induced increase in the production of purine bases (hypoxanthine, xanthine, and uric acid), the present study was performed with five healthy subjects. Intravenous administration of 300 mL 10% xylitol increased the plasma concentration and urinary excretion of purine bases, erythrocyte concentrations of adenosine monophosphate (AMP) and adenosine diphosphate (ADP), and blood concentrations of glyceraldehyde-3-phosphate (GA3P) + dihydroxyacetone phosphate (DHAP), fructose-1,6-bisphosphate (FBP), and lactic acid; it decreased the blood concentration of pyruvic acid and the plasma concentration and urinary excretion of inorganic phosphate. However, intravenous administration of 1 mg glucagon together with xylitol reduced the xylitol-induced changes in oxypurines, pyruvic acid, GABP + DHAP, and FBP, whereas it promoted the xylitol-induced increase in the urinary excretion of total purine bases and did not affect the xylitol-induced increase in the plasma concentration of total purine bases. In addition, in vitro study demonstrated that sodium pyruvate prevented the xylitol-induced degradation of adenine nucleotides in erythrocytes. These results suggested that gluconeogenesis due to glucagon increased the production of pyruvic acid, accelerated the conversion of NADH to NAD, and thereby prevented both the xylitol-induced degradation of adenine nucleotides in organs similar to erythrocytes and the inhibition of xanthine dehydrogenase in the liver and small intestine, resulting in decreases in the plasma concentration and urinary excretion of oxypurines. However, it was also suggested that in the liver storing glycogen, glucagon-induced glycogenolysis accumulated sugar phosphates, resulting in purine degradation, since the xylitol-induced increase in the NADH/NAD ratio partially blocked glycolysis at the level of GABP dehydrogenase. Therefore, administration of glucagon together with xylitol may synergistically increase purine degradation more than xylitol alone, despite decreases in the plasma concentration and urinary excretion of oxypurines.

XYLITOL (a pentose alcohol) has been used as a supplement for energy needs in patients with diabetes mellitus. However, previous studies[1,2] have demonstrated that xylitol decreases both adenine nucleotides and inorganic phosphate and causes accumulation of glycerol-3-phosphate in isolated perfused liver and isolated rat hepatocytes, indicating xylitol-induced purine degradation. Recently, we also demonstrated that xylitol increased the plasma concentration and urinary excretion of purine bases (hypoxanthine, xanthine, and uric acid), erythrocyte sugar phosphate, and erythrocyte purine degradation in humans.[3,4] In the rat liver, a main mechanism of xylitol-induced purine degradation is suggested to be the accumulation of sugar phosphate, especially glycerol-3-phosphate, and depletion of inorganic phosphate such as via fructose-induced purine degradation. It is well known that the accumulation of sugar phosphates due to phosphorylation of fructose decreases adenine nucleotide and inorganic phosphate, and a decrease in the concentration of inorganic phosphate (and adenosine triphosphate [ATP]) reverses the inhibition of ATP-degrading enzymes responsible for the irreversible breakdown of adenosine monophosphate (AMP), resulting in increased purine degradation.[5] In addition, it is suggested that in human erythrocytes the disturbance of glycolysis by xylitol causes purine degradation. Xylitol is oxidized to D-xylulose, being coupled with the conversion of NAD to NADH, while glyceraldehyde-3-phosphate (GA3P) is oxidized to 1,3-bisphosphoglycerate, being also coupled with the conversion of NAD to NADH (Fig 1). The consumption of NAD accompanied by the oxidation of xylitol to xylulose inhibits the conversion of GA3P to 1,3-bisphosphoglycerate, resulting in the accumulation of sugar phosphate, mainly GA3P + dihydroxyacetone phosphate (DHAP), which causes purine degradation.

Glucagon is well known to promote glycogenolysis in the liver. Therefore, it is possible that administration of glucagon together with xylitol produces a greater accumulation of sugar phosphate than xylitol alone, resulting in an increase in purine degradation. On the other hand, glucagon is also well known to increase gluconeogenesis, resulting in an increase in pyruvic acid production, which could protect xylitol-induced purine degradation in erythrocytes in vitro, since pyruvic acid is metabolized to lactic acid, being coupled with the conversion of NADH to NAD[3] (Fig 1). Therefore, glucagon may inhibit xylitol-induced purine degradation.

In the present study, we examined whether glucagon affects the xylitol-induced increase in the plasma concentration and urinary excretion of purine bases in humans.

SUBJECTS AND METHODS

Subjects and Protocol

Five men aged 32 to 46 years (body weight, 48 to 60 kg) participated in the study, after giving informed consent. They had normal laboratory data. After an overnight fast except for water, urine was voided completely and the first 1-hour urine samples were collected 1 hour later. The first blood samples were drawn into heparinized syringes 30 minutes before the first urine collec-

From the Third Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan.

Submitted October 30, 1995; accepted May 4, 1996.

Address reprint requests to Tetsuya Yamamoto, MD, Third Department of Internal Medicine, Hyogo College of Medicine, Mukogawa-cho 1-1, Nishinomiya, Hyogo 663, Japan.

0026-0495/96/4511-0008$03.00/0

Table 1. Blood Concentration of Glucagon and Glucose

Infusion	Before Infusion		After Beginning Infusion	
	Glucagon	Glucose	Glucagon	Glucose
Xylitol	95 ± 27	5.48 ± 0.19	93 ± 27	5.72 ± 0.15†
Xylitol + glucagon	93 ± 25	5.44 ± 0.29	14,600 ± 5,550†	7.71 ± 1.21*
Glucagon	100 ± 30	5.52 ± 0.19	15,400 ± 2,510†	8.58 ± 1.35†

NOTE. Glucagon and glucose values are expressed as pg/mL and mmol/L, respectively.

*$P < .05$, †$P < .01$: *v* before infusion.

tion. Thereafter, 300 mL 10% xylitol solution and 100 mL physiological saline containing 1 mg glucagon were infused over 1 hour. The second 1-hour urine samples were collected at the end of xylitol infusion, and the second blood samples were drawn 30 minutes after the beginning of xylitol infusion. Two weeks later, these subjects underwent the same study, except that a 1-hour infusion of 400 mL physiological saline containing 1 mg glucagon was used instead of 300 mL 10% xylitol and 100 mL physiological saline containing 1 mg glucagon. Four weeks later, with the same protocol except that 300 mL 10% xylitol and 100 mL physiological solution were used instead of 300 mL 10% xylitol solution and 100 mL physiological saline containing 1 mg glucagon, the last study was performed. During these studies, the subjects received only water so as to obtain more than 200 mL urine flow per hour.

Blood and Urine Analysis

Plasma and urinary concentrations of hypoxanthine and xanthine were determined by high-performance liquid chromatography (HPLC) with the method reported by Yamamoto et al.[6] In brief, 200 μL plasma was resuspended with 200 μL 5% perchloric acid containing 67.5 μg/mL allopurinol as the internal standard, followed by thorough mixing for 10 seconds. After centrifugation, the clear supernatant was neutralized with 1 mol/L K_2CO_3 and then injected onto a reversed-phase HPLC column (Wakosil 5C18-200, 6 × 250 mm; Wako Pure Chemical Industries, Osaka, Japan). The HPLC system consisted of an SPD-6AV UV-VIS Spectrophotometric Detector, an LC-6A Liquid Chromatograph, an SCL-6B System Controller, a C-R3A Chromatopac (all from Shimadzu, Kyoto, Japan), and a Wakosil 5C 18-200 column (Wako). The elution conditions were a mobile phase of 0.02 mol/L KH_2PO_4 (pH 2.2) and a flow rate of 1.0 mL/min. After the urine was diluted, urinary hypoxanthine and xanthine were also determined by the same method as described for determination of plasma hypoxanthine and xanthine, except for pH 4.0 instead of 2.2 in the mobile phase.

Erythrocyte concentrations of AMP, ADP, and ATP were measured by a method previously described,[7] using ion-pair reversed-phase HPLC. In brief, fresh heparinized blood was centrifuged for 10 minutes at 1,700 × *g*, and the plasma, buffy coat, and top one-fifth layer of erythrocytes were removed. The erythrocytes were washed twice with ice-cold saline and then resuspended with 2.2 vol ice-cold saline with 9-methylxanthine as the internal standard, followed by 0.8 vol 20% perchloric acid with thorough mixing for 10 seconds. After centrifugation, the clear supernatant was neutralized with 1 mol/L K_2CO_3 and then injected onto an ion-pair reversed-phase HPLC column (Wakosil 5C 18-200, 6 × 150 mm; Wako). Elution conditions were as follows: The mobile phase was 0.02 mol/L KH_2PO_4 (pH 5.2) containing 4 mmol/L tetrabutylammonium hydrogen sulfate (buffer A) and 0.02 mol/L KH_2PO_4 (pH 5.2) containing 4 mmol/L tetrabutylammonium hydrogen sulfate and 30% (vol/vol) CH_3OH (buffer B). The flow rate was 1.0 mL/min. The linear gradient elution was performed between 0 and 30 minutes; it started at 100% buffer A and ended at 20% buffer A and 80% buffer B 30 minutes later. Thereafter, the end conditions were maintained for 30 minutes.

Plasma and urinary concentrations of uric acid were measured by the uricase method using an autoanalyzer (model 736; Hitachi, Tokyo, Japan). Concentrations of lactic acid and pyruvic acid in blood were measured by enzymatic methods using a Determiner LA kit (Kiyowa Medix, Tokyo, Japan) and a Determiner PA kit (Kiyowa Medix), respectively. Concentrations of fructose-1,6-bisphosphate (FBP) and DHAP + GA3P in blood were measured as described previously.[7,8] The concentration of xylitol was measured by a method previously described,[4] and plasma glucagon was determined by radioimmunoassay using a glucagon kit (Daiichi, Tokyo, Japan).

In Vitro Study

Fresh heparinized blood was centrifuged for 10 minutes at 1,700 × *g*, and the plasma, buffy coat, and top one-fifth layer of erythrocytes were removed. The infranatant erythrocytes were washed twice with 3 vol ice-cold saline and used for in vitro studies. The incubation medium consisted of 98 mmol/L NaCl, 10 mmol/L KCl, 50 mmol/L Tris hydrochloride, 30 mmol/L glucose, 0.02 mmol/L $MgCl_2$, and 0.05 mmol/L NaH_2PO_4 in final concentration. The incubation media with xylitol alone, xylitol plus glucagon, or xylitol plus sodium pyruvate were made by adding 6 mmol/L xylitol, 6 mmol/L xylitol plus 15,000 ng/mL glucagon, or 6 mmol/L xylitol plus 0.1 mmol/L sodium pyruvate in final concentration to the incubation medium, respectively. The erythrocytes were suspended in these media to produce a hematocrit value of 15% for the suspension. Erythrocytes suspended with these media were incubated in a 4-mL tube sealed with a cap for 1 hour. The in vitro study was performed in duplicate.

Chemicals

Hypoxanthine, xanthine, glycerol-3-phosphate dehydrogenase, triose phosphate isomerase, and aldolase were purchased from Sigma Chemical (St Louis, MO). AMP, adenosine diphosphate (ADP), and ATP were purchased from Boehringer (Mannheim, Germany). Xylitol was obtained from Fuso Pharmaceuticals (To-

Table 2. Plasma Concentration of Purine Bases

Infusion	Before Infusion			After Beginning Infusion		
	Hx	X	Ua	Hx	X	Ua
Xylitol	1.84 ± 0.49	1.01 ± 0.23	321 ± 98	6.89 ± 3.18*	3.86 ± 1.23†	371 ± 111†
Xylitol + glucagon	2.04 ± 0.59	1.39 ± 0.37	320 ± 96	3.41 ± 1.25‡	2.20 ± 0.46*‡	370 ± 115*
Glucagon	1.73 ± 0.63	1.01 ± 0.24	321 ± 108	1.54 ± 0.31	1.06 ± 0.38	321 ± 117

NOTE. Values are expressed as μmol/L.

Abbreviations: Hx, hypoxanthine; X, xanthine; Ua, uric acid.

*$P < .05$, †$P < .01$: *v* before infusion.

‡$P < .05$ *v* after beginning xylitol infusion.

Table 3. Plasma Concentration of Total Purine Bases (hypoxanthine + xanthine + uric acid)

Infusion	Before Infusion	After Beginning Infusion
Xylitol	324.5 ± 99.0	382.2 ± 113.9*
Xylitol + glucagon	323.5 ± 97.2	375.9 ± 116.7*
Glucagon	324.6 ± 108.9	324.4 ± 117.4

NOTE. Values are expressed as μmol/L.
*$P < .01$ *v* before infusion.

kyo, Japan). Other chemicals were purchased from Wako Pure Chemical Industries.

Statistical Analysis

Values are shown as the mean ± SD. The significance of differences between means was analyzed by the two-tailed paired *t* test.

RESULTS

Plasma Concentrations of Xylitol, Glucagon, and Glucose

In the xylitol infusion study, the plasma concentration of xylitol was negligible and 5.87 ± 0.63 mmol/L 30 minutes before and after the beginning of the infusion, respectively. For xylitol + glucagon, it was negligible and 5.91 ± 0.36 mmol/L 30 minutes before and after the beginning of the infusion, respectively. Of course, in the glucagon infusion study, the plasma concentration of xylitol was negligible before and after the infusion. Blood concentrations of glucagon and glucose in the respective studies are shown in Table 1. Glucagon and glucose levels were elevated 30 minutes after the beginning of glucagon or xylitol + glucagon infusion. On the other hand, with the xylitol infusion, glucagon was not elevated 30 minutes after beginning the infusion, although glucose was elevated slightly.

Effect of Xylitol, Xylitol + Glucagon, or Glucagon on Plasma Concentrations and Urinary Excretion of Purine Bases

Xylitol infusion markedly increased the plasma concentration and urinary excretion of hypoxanthine, xanthine, uric acid, and total purine bases, as compared with values obtained before the infusion (Tables 2 and 3). Xylitol + glucagon infusion also increased plasma concentrations of xanthine and uric acid (Table 2) and total purine bases (Table 3) and urinary excretion of hypoxanthine, xanthine, uric acid (Table 4), and total purine bases (Table 5). It also increased the plasma concentration of hypoxanthine, but not significant (Table 2). Although the plasma concentration of total purine bases was not different for xylitol infusion and xylitol + glucagon infusion, plasma concentrations of hypoxanthine and xanthine with the xylitol + glucagon infusion were less than the respective values obtained with the xylitol infusion (Table 2). Glucagon infusion did not affect plasma concentrations of hypoxanthine, xanthine, uric acid, and total purine bases or urinary excretion of hypoxanthine and xanthine (Tables 2 to 5). However, it increased the urinary excretion of uric acid and total purine bases (Tables 4 and 5).

Effect of Xylitol, Xylitol + Glucagon, or Glucagon on Erythrocyte Adenine Nucleotides and Blood Glycolytic Intermediates

Xylitol infusion increased erythrocyte concentrations of AMP and ADP but did not affect ATP levels (Table 6). Xylitol + glucagon or glucagon infusion did not affect erythrocyte concentrations of AMP, ADP, and ATP (Table 6). Blood concentrations of GA3P + DHAP, FBP, and lactic acid were increased by xylitol infusion (Table 7), whereas the blood concentration of pyruvic acid was decreased (Table 8). In contrast, blood concentrations of GA3P + DHAP and FBP were not increased by xylitol + glucagon or glucagon infusion (Table 7). The blood concentration of lactic acid was increased by xylitol + glucagon infusion, but pyruvic acid was not increased, whereas blood concentrations of pyruvic acid and lactic acid were increased by glucagon infusion (Table 8).

Effect of Xylitol, Xylitol + Glucagon, or Glucagon on Plasma Concentration and Urinary Excretion of Inorganic Phosphate

Xylitol infusion decreased the plasma concentration of inorganic phosphate from 0.98 ± 0.08 mmol/L 30 minutes before the infusion to 0.74 ± 0.11 mmol/L 30 minutes after beginning the infusion ($P < .05$), and xylitol + glucagon infusion decreased the plasma concentration of inorganic phosphate from 1.00 ± 0.10 mmol/L 30 minutes before the infusion to 0.55 ± 0.13 mmol/L 30 minutes after beginning the infusion ($P < .01$). Glucagon infusion also decreased the plasma concentration of inorganic phosphate from 0.99 ± 0.20 mmol/L 30 minutes before the infusion to 0.76 ± 0.10 mmol/L 30 minutes after beginning the infusion ($P < .05$). On the other hand, xylitol infusion decreased the urinary excretion of inorganic phosphate from 0.68 ± 0.18 mmol before the infusion to 0.49 ± 0.22 mmol after beginning the infusion ($P < .01$), and xylitol + glucagon infusion did not affect urinary excretion of inorganic phosphate (0.73 ± 0.24 mmol before the infusion and 0.70 ± 0.24 mmol after beginning the infusion). Glucagon infusion increased the urinary excretion of inorganic phosphate

Table 4. Urinary Excretion of Purine Bases

Infusion	Before Infusion			After Beginning Infusion		
	Hx	X	Ua	Hx	X	Ua
Xylitol	5.25 ± 2.36	4.77 ± 2.41	138 ± 40	48.66 ± 19.36*	15.09 ± 2.66†	206 ± 69*
Xylitol + glucagon	5.72 ± 2.65	5.29 ± 1.48	146 ± 65	18.11 ± 4.57*‡	11.07 ± 3.17†‡	356 ± 114†
Glucagon	7.37 ± 3.51	5.15 ± 0.65	148 ± 38	6.60 ± 2.63	5.18 ± 1.07	254 ± 36†

NOTE. Values are expressed as μmol. Hx, X, Ua, and statistical symbols are as defined in Table 2.

Table 5. Urinary Excretion of Total Purine Bases (hypoxanthine + xanthine + uric acid)

Infusion	Before Infusion	After Beginning Infusion
Xylitol	147.0 ± 43.1	269.1 ± 53.1*
Xylitol + glucagon	157.0 ± 68.0	385.0 ± 114.6*†
Glucagon	160.0 ± 41.5	265.7 ± 38.9*

NOTE. Values are expressed as μmol/L.
*$P < .01$ *v* before infusion.
†$P < .05$ *v* after beginning xylitol infusion.

from 0.67 ± 0.16 mmol before the infusion to 0.96 ± 0.34 mmol after beginning the infusion ($P < .05$).

In Vitro Effect of Xylitol, Xylitol + Glucagon, or Glucagon on AMP, ADP, GA3P + DHAP, and Hypoxanthine

In the in vitro incubation study, 6 mmol/L xylitol increased the medium concentration of hypoxanthine 1.4-fold and the erythrocyte concentration of AMP 2.5-fold, ADP 1.6-fold, and GA3P + DHAP 2.5-fold compared with the respective control values; 6 mmol/L xylitol + 15,000 ng/mL glucagon increased these values to the same degree as xylitol. However, 6 mmol/L xylitol + 0.1 mmol/L sodium pyruvate increased the medium concentration of hypoxanthine 1.08-fold and the erythrocyte concentration of AMP 1.1-fold, ADP 1.1-fold, and GA3P + DHAP 1.2-fold compared with the respective control values. These results indicate that sodium pyruvate prevented xylitol-induced purine degradation in erythrocytes.

DISCUSSION

The present study demonstrated that xylitol infusion increases the urinary excretion and plasma concentration of oxypurines and uric acid (Tables 2 to 5), erythrocyte concentrations of AMP and ADP (Table 6), and blood concentrations of GA3P + DHAP and FBP (Table 7). On the other hand, it decreases the blood concentration of pyruvic acid (Table 8), as described previously.[4] It was also demonstrated that glucagon infusion increases the urinary excretion of uric acid (Table 4) but does not increase the plasma concentration of uric acid or the urinary excretion or plasma concentration of oxypurines (Tables 2 and 4). However, the most intriguing results are that the increases in the urinary excretion and plasma concentration of oxypurines with xylitol + glucagon infusion were smaller than the respective increases obtained with xylitol infusion (Tables 2 and 4). Similar results were obtained for erythrocyte concentrations of AMP and ADP and blood concentrations of GA3P + DHAP, respectively (Tables 6 and 7).

Table 7. Erythrocyte Concentration of GA3P + DHAP and FBP

Infusion	Before Infusion		After Beginning Infusion	
	GA3P + DHAP	FBP	GA3P + DHAP	FBP
Xylitol	17.1 ± 5.1	5.3 ± 0.7	70.1 ± 28.5*	14.2 ± 6.4*
Xylitol + glucagon	16.6 ± 4.1	5.2 ± 0.7	20.9 ± 3.7	7.2 ± 1.9
Glucagon	19.1 ± 5.1	6.1 ± 1.2	20.0 ± 4.9	5.8 ± 0.9

NOTE. Values are expressed as nmol/mL erythrocytes.
*$P < .05$ *v* before infusion.

Previously, we demonstrated that xylitol disturbed glycolysis via its metabolism at the site of GA3P to 1,3-bisphosphoglycerate, and thereby GA3P + DHAP and FBP are accumulated[3] (Fig 1). This also appears to be the mechanism in other tissues similar to erythrocytes, since xylitol is rapidly taken up by these tissues. Furthermore, xylitol itself is metabolized to xylulose and then to xylulose-5-phosphate, fructose-6-phosphate, and glycerol-3-phosphate in liver (Fig 1). Therefore, an abrupt increase in these organic phosphates seems to have accelerated the degradation of adenine nucleotides in liver, subsequently increasing the plasma concentration and urinary excretion of purine bases and decreasing the plasma concentration and urinary excretion of inorganic phosphate in the present study. Although xylitol must be considered an enhancer of purine synthesis, it seems to play a minor role in increasing the plasma concentration and urinary excretion of purine bases, since a loss of adenine nucleotides by xylitol was observed in isolated perfused liver.[1] Besides acceleration of purine degradation, we recently observed that xylitol infusion inhibited xanthine dehydrogenase activity via the metabolism of xylitol in humans,[4] using the oxidation of pyrazinoic acid to 5-hydroxypyrazinoic acid by xanthine dehydrogenase. The oxidation of xylitol to D-xylulose is coupled with the conversion of NAD to NADH (Fig 1), an increase in the cytosolic concentration of which directly inhibits xanthine dehydrogenase activity.[4,9] Therefore, the xylitol-induced increase in the plasma concentration and urinary excretion of oxypurines is attributable to accelerated purine degradation and xanthine dehydrogenase inhibition, and the xylitol-induced increase in the plasma concentration of uric acid is attributable to accelerated purine degradation. On the other hand, since glucagon increases glycogenolysis in the liver using ATP as a phosphate donor, levels of glycolytic intermediates containing phosphate abruptly increase in patients with von Gierke's disease, in whom the production of glucose from glucose-6-phosphate is inhibited because of a deficiency of glucose-6-phosphatase. This abrupt increase in these organic phos-

Table 6. Erythrocyte Concentration of Adenine Nucleotides

Infusion	Before Infusion			After Beginning Infusion		
	AMP	ADP	ATP	AMP	ADP	ATP
Xylitol	13.0 ± 1.8	214 ± 17	1,718 ± 165	37.8 ± 12.5*	342 ± 60*	1,502 ± 144
Xylitol + glucagon	12.8 ± 2.3	231 ± 7	1,689 ± 158	18.11 ± 4.57	253 ± 6	1,543 ± 79
Glucagon	12.9 ± 1.2	218 ± 19	1,603 ± 156	11.6 ± 1.8	211 ± 19	1,578 ± 183

NOTE. Values are expressed as nmol/mL erythrocytes.
*$P < .05$ *v* before infusion.

Table 8. Blood Concentration of Lactic Acid and Pyruvic Acid

Infusion	Before Infusion		After Beginning Infusion	
	Lactic Acid	Pyruvic Acid	Lactic Acid	Pyruvic Acid
Xylitol	0.85 ± 0.23	0.061 ± 0.009	0.98 ± 0.23†	0.039 ± 0.015*
Xylitol + glucagon	0.76 ± 0.32	0.061 ± 0.016	1.00 ± 0.39†	0.055 ± 0.012
Glucagon	0.81 ± 0.15	0.068 ± 0.017	0.98 ± 0.17*	0.090 ± 0.023*

NOTE. Values are expressed as mmol/L. Statistical symbols are as defined in Table 2.

phates accelerates the degradation of adenine nucleotides in patients with von Gierke's disease.[10] In the present study, glucagon decreased the plasma concentration but increased urinary excretion of inorganic phosphate in normal subjects. Accordingly, a decrease in the plasma concentration of inorganic phosphate may be attributed to an increase in urinary excretion of inorganic phosphate. In addition, glucagon did not affect the plasma concentration of purine bases (Table 2) or the urinary excretion of oxypurines (Table 3), although it increased the urinary excretion of uric acid (Table 3), as described previously.[11] Therefore, it is suggested that in normal subjects glucagon-induced purine degradation is negligible. The plasma concentration of xylitol in the xylitol infusion did not differ from that in the xylitol + glucagon infusion, suggesting that glucagon did not disturb the intracellular uptake of xylitol but did affect its intracellular metabolism.

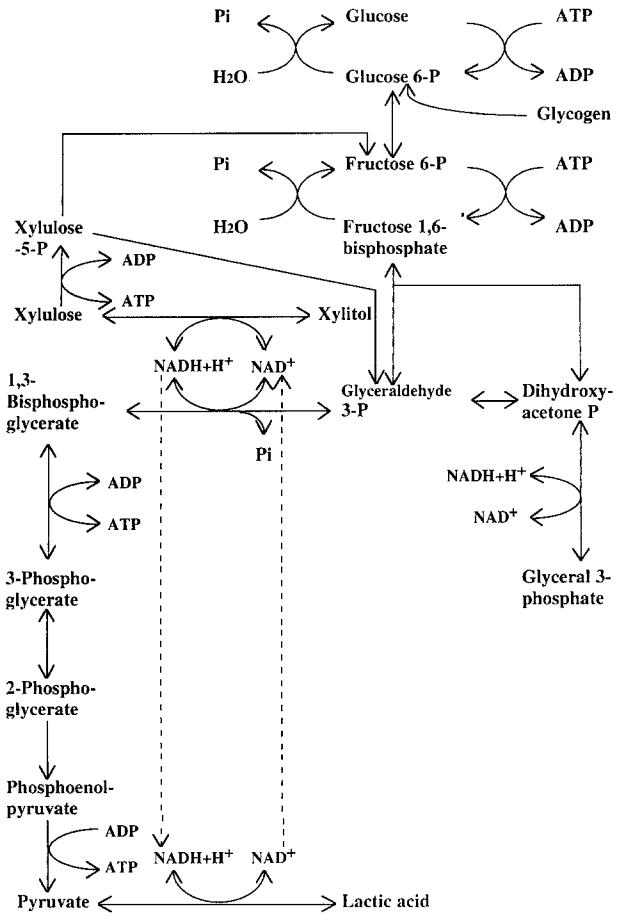

Fig 1. Glycolysis and xylitol oxidation. Glucagon accelerates dotted-line flow (→) by producing pyruvic acid.

The following two questions arise: How did glucagon reduce xylitol-induced increases in the plasma concentration and urinary excretion of oxypurines? And furthermore, although glucagon reduced xylitol-induced increases in the plasma concentration and urinary excretion of oxypurines, why did it not reduce the xylitol-induced increase in the plasma concentration of total purine bases? Besides glycogenolysis, glucagon promotes gluconeogenesis from glycolytic intermediates and amino acids. Accordingly, via gluconeogenesis, it increases the production of pyruvic acid, as indicated by an increase in the blood concentration of pyruvic acid in the glucagon infusion study (Table 6). An increase in the concentration of pyruvic acid may accelerate the reduction of pyruvic acid to lactic acid by lactic dehydrogenase, being coupled with the conversion of NADH to NAD (Fig 1). An increase in the concentration of NAD may reduce xylitol-induced purine degradation in many organs besides the liver, and a decrease in the concentration of NADH may reverse the xylitol-induced inhibition of xanthine dehydrogenase activity in both the liver and the small intestine possessing xanthine dehydrogenase. These mechanisms seem to explain sufficiently why glucagon reduces the xylitol-induced increase in the plasma concentration and urinary excretion of oxypurines. However, the effect of glucagon on the xylitol-induced increase in the plasma concentration and urinary excretion of total purine bases seems to be different from that of oxypurines. With xylitol administration, xylitol is converted to xylulose, which is then converted to xylulose-5-phosphate. The conversion of xylitol to xylulose causes an increase in the NADH/NAD ratio, which partially inhibits glycolysis in the liver at the level of GA3P to 1,3-bisphosphoglycerate. Since glucagon promotes glycogenolysis in the liver storing glycogen, more sugar phosphates were accumulated in the xylitol + glucagon infusion than in the xylitol infusion. Therefore, it is suggested that administration of glucagon with xylitol promotes purine degradation in the liver, resulting in increased total purine base production, although glucagon seems to decrease xylitol-induced purine degradation in other organs similar to erythrocytes and xylitol-induced inhibition of xanthine dehydrogenase in the liver and small intestine. Although these hypotheses are supported by the results obtained in the present study and previous studies, including the in vitro study, other unknown effect(s) of glucagon may have played a role in the present results. Therefore, further study is needed to clarify all the mechanisms involved.

REFERENCES

1. Woods HF, Krebs HA: Xylitol metabolism in the isolated perfused rat liver. Biochem J 134:437-443, 1973

2. Vincent MF, Van den Berghe G, Hers HG: D-Xylulose–induced depletion of ATP and P_i and increase in PRPP in isolated rat hepatocytes. Adv Exp Med Biol 253A:317-323, 1989

3. Yamamoto T, Moriwaki Y, Suda M, et al: Xylitol-induced increase in purine degradation: A role of erythrocytes. Int J Clin Pharmacol Ther 31:35-39, 1993

4. Yamamoto T, Moriwaki Y, Takahashi S, et al: Xylitol-induced increase in the concentration of oxypurines and its mechanism. Int J Clin Pharmacol Ther 33:360-365, 1995

5. Fox IH: Metabolic bases for disorders of purine nucleotide degradation. Metabolism 30:616-634, 1981

6. Yamamoto T, Moriwaki Y, Takahashi S, et al: Ethanol as a xanthine dehydrogenase inhibitor. Metabolism 44:779-785, 1995

7. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effect of ethanol ingestion on nucleotides and glycolytic intermediates in erythrocytes and purine bases in plasma and urine: Acetaldehyde-induced erythrocyte purine degradation. Metabolism 42:1212-1215, 1993

8. Minakami S, Suzuki C, Saito T, et al: Studies on erythrocyte glycolysis. I. Determination of the glycolytic intermediates in human erythrocytes. J Biochem 58:543-550, 1965

9. Kaminski ZW, Jezewska MM: Effect of NADH on hypoxanthine hydroxylation by native NAD^+-dependent xanthine oxidoreductase of rat liver, and the possible biologic role of this effect. Biochem J 200:597-603, 1981

10. Cohen JL, Vinik A, Faller J, et al: Hyperuricemia in glycogen storage disease type I. Contributions by hypoglycemia and hyperglucagonemia to increased urate production. J Clin Invest 75:251-257, 1985

11. Role TF, Kogut MD: The pathogenesis of hyperuricemia in glycogen storage disease, type I. Pediatr Res 11:664-669, 1977