Effect of Glucose on the Plasma Concentration and Urinary Excretion of Uridine and Purine Bases

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

To examine whether glucose increases the plasma concentration of purine bases and uridine, 75 g glucose was administered orally to eight healthy subjects and two patients with hyperuricemia. The plasma concentration of uridine increased by 21%, 25%, and 20% 30, 60, and 90 minutes after administration of glucose, respectively. However, urinary excretion of uridine was not affected, nor were the plasma concentrations and urinary excretion of purine bases (hypoxanthine, xanthine, and uric acid). These results suggest that the glucose-induced increase in plasma uridine was not concomitant with adenosine triphosphate (ATP) consumption–induced purine degradation, but instead was ascribable to a uridine diphosphate (UDP)-glucose consumption–induced pyrimidine degradation (UDP-glucose → UDP → uridine monophosphate [UMP] → uridine).

AFTER GLUCOSE is administered orally, it is actively absorbed from the intestinal tract and either used as energy or stored as glycogen in the body. In the former, the absorbed glucose is phosphorylated to glucose-6-phosphate by glucokinase using adenosine triphosphate (ATP) as a phosphate donor and metabolized via glycolysis and subsequent oxidation of pyruvate to produce ATP. In the latter, glucose-6-phosphate is converted to glucose-1-phosphate, from which glycogen is formed, using uridine triphosphate (UTP). Since the consumption of ATP and UTP, as well as production of ATP, is prompted by the metabolism of glucose, glucose metabolism may affect the plasma concentration of purine bases and uridine, which are the respective degradation products of ATP and UTP.

However, there is no known previous study regarding the effect of oral administration of glucose on the plasma concentration and urinary excretion of oxypurines and uridine in normal subjects, although a few studies[1,2] have demonstrated that glucose does not increase plasma uric acid in normal subjects but does increase it in patients with non–insulin-dependent diabetes mellitus. On the other hand, the mechanism of fructose (the isomer of glucose)-induced purine and pyrimidine degradation has been demonstrated by many previous studies.[3-5] In short, fructose is also phosphorylated to fructose-1-phosphate by hexokinase using ATP. However, since phosphate sugars are abruptly accumulated, ATP is rapidly consumed. Fructose-induced ATP consumption increases the concentration of adenosine diphosphate and adenosine monophosphate (AMP) in the liver, accelerating purine degradation (AMP → inosine monophosphate → inosine → hypoxanthine → xanthine → uric acid). In addition, ATP consumption decreases the conversion of uridine diphosphate (UDP) to UTP to use ATP as a phosphate donor, resulting in an increased concentration of UDP in the liver, which enhances pyrimidine degradation (UDP → uridine monophosphate [UMP] → uridine).

Based on this background information, we performed the present study using oral administration of 75 g glucose to determine whether glucose affects the plasma concentration and urinary excretion of purine bases and uridine, and further investigated the difference between the effect of glucose versus fructose on purine and pyrimidine metabolism.

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

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Address reprint requests to Tetsuya Yamamoto, MD, Third Department of Internal Medicine, Hyogo College of Medicine, Mukogawa-cho 1-1, Nishinomiya, Hyogo 663-8501, Japan.

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SUBJECTS AND METHODS

Subjects and Protocol

Ten men aged 43 ± 5 (mean ± SD) years (body weight, 53 to 68 kg; eight healthy subjects and two patients with hyperuricemia) participated in the study after provision of informed consent. They had normal laboratory data. After an overnight fast except for water, urine was voided completely, and thereafter, urine samples were collected every hour for 3 hours. After the first 1-hour urine collection, 300 mL 25% glucose solution was ingested. Blood samples were drawn 30 minutes before the first urine collection and 30, 60, 90, and 120 minutes after the ingestion of glucose. Two weeks later, the control study was performed using the same protocol except for administration of 300 mL water only instead of 300 mL water containing glucose.

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] The plasma uridine concentration was also determined by HPLC with the method reported by Yamamoto et al.[6] Urinary uridine was determined as follows. The chromatograph consisted of two CCPM pumps, an SC-8020 system controller, two spectrophotometric detectors (UV-8010 and UV-8020), and a VC-8020 column-switching valve (all from Tosoh, Tokyo, Japan). The chromatographic analysis used a Wakosil 5C18-200 (4.6 × 250 mm; Wako Pure Chemicals, Osaka, Japan) as the first column and a Tosoh TSK Gel (ODS-80A, 4.6 × 250 mm) as the second column. In both columns, the mobile phase was 20 mmol/L KH_2PO_4 (pH 4.7), the flow rate 1 mL/min, and the detection wavelength 254 nm. At the fraction time in which uridine was eluted via the first column, the two columns were connected and the elute was monitored from the second column. 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 were determined by a Determiner LA kit and Determiner PA kit (Kyowa Medix, Tokyo, Japan), respectively. Plasma concentrations of insulin and glucagon were determined by a radioimmunoassay using a Glucagon kit (Daiichi, Tokyo, Japan) and an Insulin Riabead II kit (Dinabot, Tokyo, Japan), respectively.

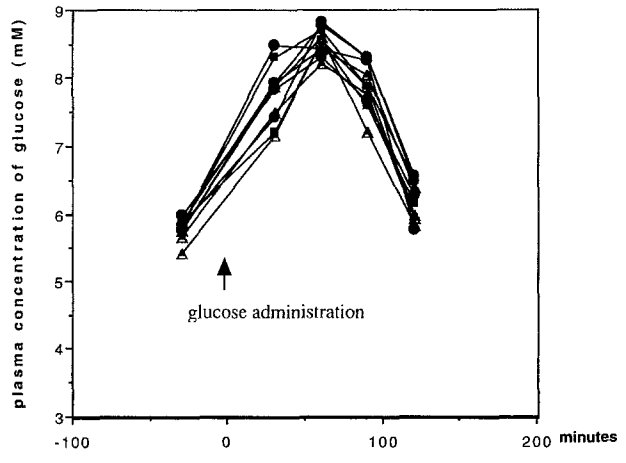

Fig 1. Plasma concentration of glucose before and after oral administration of 75 g glucose.

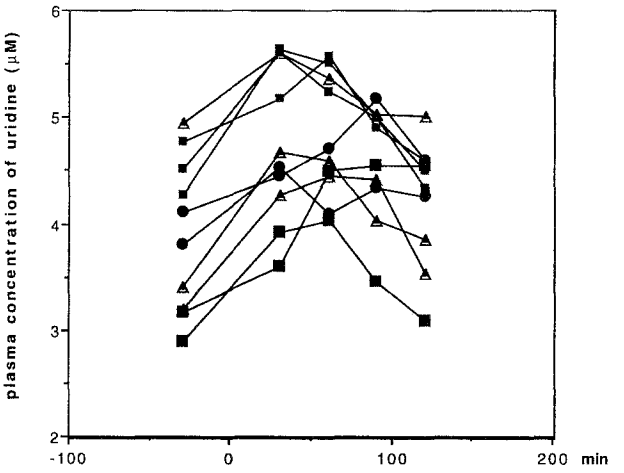

Fig 2. Plasma concentration of uridine before and after oral administration of 75 g glucose.

Statistical Analysis

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

RESULTS

Plasma Glucose

The plasma concentration of glucose was 5.79 ± 0.15, 7.78 ± 0.44, 8.55 ± 0.20, 7.91 ± 0.36, and 6.19 ± 0.29 mmol/L just before and 30, 60, 90, and 120 minutes after administration of glucose, respectively. It increased significantly after glucose administration ($P < .01$). None of the subjects showed a diabetic pattern (Fig 1). On the other hand, the plasma glucose concentration did not change in the control study (5.74 ± 0.10, 5.78 ± 0.08, 5.79 ± 0.11, 5.78 ± 0.12, and 5.78 ± 0.13 mmol/L just before and 30, 60, 90, and 120 minutes after administration of water only, respectively).

Effect of 75 g Glucose on Plasma Uridine and Purine Bases

Thirty, 60, 90, and 120 minutes after administration of glucose, plasma uridine increased by 21%, 25%, 20%, and 10%, respectively, compared with the baseline value. (Fig 2 and Table 1). In contrast, glucose administration did not affect the plasma concentration of hypoxanthine, xanthine, or uric acid significantly. In the control study, plasma hypoxanthine, xanthine, uric acid, and uridine did not change (Table 1).

Effect of 75 g Glucose on Urinary Excretion of Purine Bases and Uridine

Glucose administration did not significantly affect the urinary excretion of hypoxanthine, xanthine, uric acid, or uridine. In the control study, urinary excretion of hypoxanthine, xanthine, uric acid, and uridine also did not change (Table 2).

Effect of 75 g Glucose on Plasma Glucagon and Insulin

Thirty, 60, 90, and 120 minutes after administration of glucose, plasma insulin increased 6.4-, 9.1-, 11.2-, and 9.0-fold compared with the baseline value, while the plasma glucagon concentration did not change. On the other hand, plasma insulin and glucagon did not change significantly in the control study (Table 3).

Effect of 75 g Glucose on Blood Lactic Acid and Pyruvic Acid and Plasma Inorganic Phosphate

The blood concentration of lactic acid increased by 45% 90 minutes after administration of glucose compared with the baseline value. Thirty, 60, and 90 minutes after glucose

Table 1. Plasma Concentration of Purine Bases and Uridine (μmol/L) Before and After Glucose or Water (mean ± SD, N = 10)

Treatment	Before	After			
		30 min	60 min	90 min	120 min
Glucose					
Hypoxanthine	1.75 ± 0.52	1.81 ± 0.60	1.85 ± 0.64	1.74 ± 0.50	1.53 ± 0.57
Xanthine	0.91 ± 0.29	0.93 ± 0.30	1.02 ± 0.37	0.97 ± 0.35	0.95 ± 0.30
Uric acid	382 ± 86	381 ± 84	380 ± 83	380 ± 84	380 ± 83
Uridine	3.92 ± 0.72	4.75 ± 0.73*	4.82 ± 0.57†	4.59 ± 0.54*	4.24 ± 0.57
Control (water)					
Hypoxanthine	1.70 ± 0.49	1.74 ± 0.47	1.68 ± 0.49	1.79 ± 0.50	1.73 ± 0.47
Xanthine	0.85 ± 0.24	0.85 ± 0.22	0.86 ± 0.22	0.85 ± 0.23	0.86 ± 0.23
Uric acid	377 ± 83	376 ± 82	377 ± 81	377 ± 84	376 ± 82
Uridine	4.03 ± 0.61	4.01 ± 0.61	4.05 ± 0.60	3.98 ± 0.56	3.97 ± 0.58

*$P < .05$.
†$P < .01$.

Table 2. Urinary Excretion of Purine Bases and Uridine (μmol/hr) Before and After Glucose or Water (mean ± SD, N = 10)

Treatment	Urine Sample		
	First	Second	Third
Glucose			
Hypoxanthine	5.72 ± 1.79	5.43 ± 1.83	5.17 ± 2.13
Xanthine	5.40 ± 1.48	5.29 ± 2.11	5.21 ± 2.50
Uric acid	183 ± 47	176 ± 55	182 ± 64
Uridine	0.12 ± 0.02	0.12 ± 0.03	0.12 ± 0.02
Control (water)			
Hypoxanthine	5.85 ± 1.51	5.77 ± 1.31	5.80 ± 1.41
Xanthine	5.24 ± 1.54	5.46 ± 1.71	5.33 ± 1.82
Uric acid	173 ± 48	174 ± 46	175 ± 48
Uridine	0.11 ± 0.03	0.12 ± 0.02	0.13 ± 0.02

NOTE. First, second, and third denote the 1-hour urine before treatment, 1-hour urine after treatment, and 1-hour urine after the collection of the second urine.

administration, the blood concentration of pyruvic acid also increased by 33%, 33%, and 44%, respectively. However, glucose did not significantly affect the plasma concentration of inorganic phosphate. In the control study, the concentration of lactic acid and pyruvic acid in blood and inorganic acid in plasma did not change significantly (Table 4).

DISCUSSION

In the present study, oral glucose administration did not increase the plasma concentration or urinary excretion of purine bases (hypoxanthine, xanthine, and uric acid; Tables 1 and 2), suggesting that glucose does not affect purine degradation. It was also demonstrated that glucose administration increases the concentration of glucose and insulin in plasma and lactate and pyruvate in blood (Tables 3 and 4), although inorganic phosphate in plasma was not significantly decreased (Table 4). These results indicate that administration of glucose enhances glucose uptake by insulin and also accelerates glycolysis in cells to produce ATP. This is compatible with the results of a previous study in which oral administration of glucose (1 g/kg body weight) increased ATP by 10% and lactate by 130% in the liver of fasted rats.[7] However, in the present study, the most intriguing result is that glucose administration increased the plasma concentration of uridine.

Although pyrimidine degradation is concomitant with ATP consumption–induced purine degradation, resulting in an increased plasma concentration of uridine,[2,8-12] the present results do not indicate ATP consumption–induced purine degradation

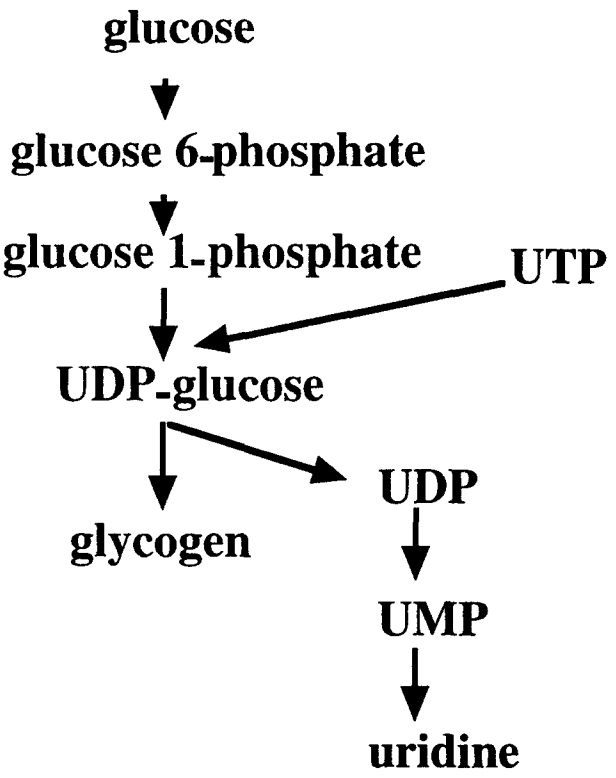

Fig 3. Scheme of hypothetical mechanism of glucose-induced increase in plasma uridine.

upon glucose administration. Therefore, a glucose-induced increase in the plasma concentration of uridine was not ascribable to ATP consumption, which develops with fructose infusion, xylitol infusion, ethanol ingestion, ischemia, or muscular exercise.[3,8-12] The question arises as to what causes the increase in the plasma concentration of uridine induced by administration of glucose. One possibility is that an increase in plasma uridine is ascribable to decreases in the urinary excretion and/or intracellular uptake of uridine. However, administration of glucose did not affect urinary excretion of uridine in the present study. Also, an increase in plasma insulin due to administration of glucose, without a change in the glucagon level, may decrease plasma uridine, since insulin and glucagon accelerate the sodium-dependent nucleoside transport of uridine to the intracellular space in vitro.[13] Therefore, decreases in the urinary excretion and/or intracellular uptake of uridine do not seem to play a role in the increase of plasma uridine. Another

Table 3. Plasma Concentration of Insulin (μU/mL) and Glucagon (pg/mL) Before and After Glucose or Water (mean ± SD, N = 10)

Treatment	Before	After			
		30 min	60 min	90 min	120 min
Glucose					
Insulin	8.2 ± 5.2	52.7 ± 33.3*	75.0 ± 39.0*	92.1 ± 41.7*	73.5 ± 49.1*
Glucagon	128 ± 40	119 ± 57	120 ± 44	123 ± 44	123 ± 47
Control (water)					
Insulin	8.9 ± 4.5	8.1 ± 3.6	9.2 ± 4.5	9.4 ± 4.6	8.4 ± 3.7
Glucagon	129 ± 33	130 ± 27	129 ± 35	130 ± 38	131 ± 38

*$P < .01$.

Table 4. Blood Concentration of Lactic Acid, Pyruvic Acid, and Inorganic Phosphate (μmol/L) Before and After Glucose or Water (mean ± SD, N = 10)

Treatment	Before	After			
		30 min	60 min	90 min	120 min
Glucose					
Lactic acid	1.23 ± 0.39	1.38 ± 0.37	1.60 ± 0.26*	1.78 ± 0.36†	1.34 ± 0.32
Pyruvic acid	0.09 ± 0.03	0.12 ± 0.03	0.12 ± 0.03*	0.13 ± 0.03†	0.10 ± 0.02
Inorganic phosphate	0.94 ± 0.14	ND	0.90 ± 0.13	ND	0.83 ± 0.12
Control (water)					
Lactic acid	1.13 ± 0.28	1.19 ± 0.24	1.14 ± 0.22	1.19 ± 0.23	1.20 ± 0.22
Pyruvic acid	0.08 ± 0.02	0.08 ± 0.02	0.09 ± 0.02	0.08 ± 0.02	0.08 ± 0.02
Inorganic phosphate	0.94 ± 0.12	ND	0.95 ± 0.13	ND	0.98 ± 0.11

Abbreviation: ND, not determined.
*$P < .05$.
†$P < .01$.

possibility is that an increase in plasma uridine is ascribable to enhanced production of uridine. When glucose is administered during fasting, the liver switches from glucose production to glucose uptake, glycogenesis begins, and glycogen is synthesized. In glycogenesis, glucose is phosphorylated to glucose-6-phosphate using ATP and is then converted to glucose-1-phosphate. In the next step, uridine diphosphoglucose (UDP-glucose) is formed from glucose-1-phosphate and UTP, and in the final step, glycogen is synthesized from UDP-glucose together with UDP release (Fig 3). A previous study[7] demonstrated that glucose administered by oral gavage increased the liver concentration of glucose by about 100% and glucose-6-phosphatase by about 50% and decreased the liver concentration of UDP-glucose by about 50% (0.229 ± 0.02 *v* 0.110 ± 0.01 mmol/g wet weight, before *v* after oral glucose), indicating that glucose enhances glycogenesis, as well as suggesting that UDP-glucose is used excessively in enhanced glycogenesis, resulting in decreased UDP-glucose.

Therefore, the present study (glucose-induced increase in plasma uridine) suggests that UDP release from UDP-glucose abruptly increases via glycogenesis after oral administration of glucose, leading to UDP degradation (UDP → UMP → uridine). If true, it seems clinically important that an increase in the plasma concentration of uridine may reflect the degree of glycogenesis in an oral glucose tolerance test. Therefore, further examination is needed to clarify the mechanism of glucose-induced pyrimidine degradation during an oral glucose tolerance test.

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