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Effects of sucrose on plasma concentrations and urinary excretion of purine bases

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Abstract

To determine whether an increase in the plasma concentration of uric acid by sucrose intake is ascribable to enhanced purine degradation and/or decreased urinary excretion of uric acid, we measured the plasma concentrations of purine bases (uric acid, hypoxanthine, and xanthine) and uridine, as well as the urinary excretion of purine bases in 7 healthy subjects before and after administering sucrose at 1.5 g/kg of body weight in 2 related experiments, with and without an administration of 300 mg of allopurinol. In addition, in the control experiment without an administration of sugar and with an administration of 300 mg of allopurinol, we measured the same parameters in those 7 subjects. Without added allopurinol, sucrose increased the plasma concentration of uric acid by 11% ($P < .01$) as well as that of uridine, although it did not significantly increase the plasma concentrations of hypoxanthine and xanthine or the urinary excretion of uric acid. On the other hand, the plasma concentration and urinary excretion of hypoxanthine were increased by 2.4-fold ($P < .05$) and 3.42-fold ($P < .05$), respectively, and the plasma concentration of xanthine was increased by 1.2-fold ($P < .05$) together with an increase in the plasma concentration of uridine in the experiment with allopurinol administration. In contrast, the plasma concentration and urinary excretion of uric acid and the urinary excretion of xanthine were not increased. In addition, in the control experiment, all parameters did not change significantly. These results indicate that purine degradation enhanced by sucrose plays a major role in the increased plasma concentration of uric acid.
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1. Introduction

Sucrose, ingested in excessive amounts by large numbers of people in urbanized countries, is known to be a cause of obesity, and it is known to stimulate insulin secretion. Both obesity and hyperinsulinemia are closely related to hyperuricemia, and previous studies have suggested that obesity and hyperinsulinemia decrease uric acid clearance, leading to hyperuricemia [1-3].

Sucrose is a disaccharide made up of fructose and glucose, and it is well known that fructose enhances adenine nucleotide degradation, leading to an increase in the plasma concentration of uric acid [4-8]. Furthermore, it has been reported that as the rate of fructose infusion increases, the serum concentration of urate is also increased [5]. Glucose stimulates the secretion of insulin, and it has been speculated that sucrose enhances adenine nucleotide degradation and decreases uric acid clearance. Sucrose may also play an important role in hyperuricemia because it is separated by α-glucosidase into fructose and glucose, which are rapidly absorbed by the small intestine. A previous study demonstrated that ingestion of large amounts of sucrose over a 2-week period increased the serum concentration of uric acid and decreased the fractional excretion of uric acid, suggesting that a decrease in urinary excretion of uric acid by sucrose causes an increase in the serum concentration of urate [6]. Another study found that ingestion of 1.0 g of sucrose per kilogram of body weight increased the level of uric acid in serum and suggested that the fructose component of sucrose increased purine degradation [7]. However, it has not been clarified whether sucrose enhances purine degradation in humans.

Recent studies have shown that purine degradation, such as adenine nucleotide degradation induced by ethanol and exercise, markedly increases the level of plasma oxypurines in subjects treated with allopurinol, a xanthine oxidase

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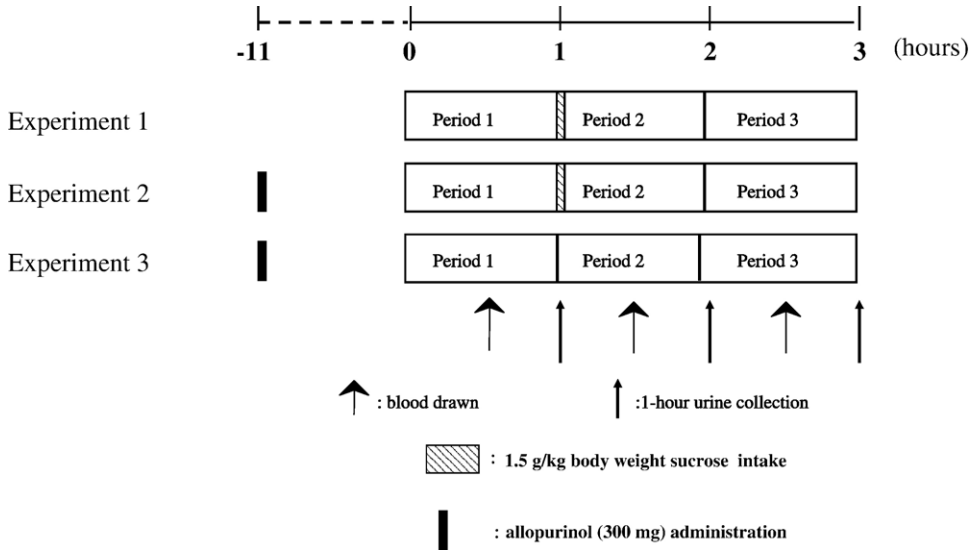

Fig. 1. Experimental protocol.

inhibitor, indicating that oxypurines are sensitive markers of purine degradation [8]. Therefore, to identify sucrose-induced purine degradation, we conducted the present study using sucrose and allopurinol. In addition, we examined whether sucrose has an effect on the renal clearance of uric acid as sucrose-induced hyperinsulinemia and hyperlactatemia may cause its decrease.

2. Subjects and methods

Seven healthy males were enlisted as subjects (age, 36.4 ± 3.0 years old; weight, 64.9 ± 5.2 kg; height, 170.0 ± 4.4 cm) after providing informed consent. Each had normal laboratory data, including serum aspartate aminotransferase, alanine aminotransferase, creatinine, uric acid, and plasma glucose. The experimental protocols are shown in Fig. 1. In experiment 1, after an overnight fast except for water, urine was completely voided at 8:00 AM. Thereafter, urine was collected every hour for a total of 3 times (periods 1, 2, and 3), and blood was drawn at the midpoint of each of those 1-hour collection periods. After the period 1 urine collection, 200 mL of water containing sucrose at a ratio of 1.5 g/kg of body weight was administered over a period of 2 minutes. Two weeks later, experiment 2 was performed with the same protocol, except that 11 hours before voiding morning urine, allopurinol (300 mg) was administered to inhibit xanthine dehydrogenase because allopurinol is completely converted to oxypurinol within 11 hours after its administration [8]. Two weeks after experiment 2, the control experiment (experiment 3) was performed with the same experiment protocol as used in experiment 2, except for without the administration of sucrose. The concentrations of uric acid in plasma and urine were determined using a Wako Uric Acid Kit (Wako Pure Chemical, Osaka, Japan), whereas those of hypoxanthine, xanthine, and oxypurinol in plasma and urine, and uridine in plasma were measured by high-performance liquid chromatography, as described previously [8]. In addition, the blood concentration of lactic acid was determined as described previously [8].

The concentrations of glucose were measured by glucose oxidase method and those of insulin in plasma were measured by a solid-phase radioimmunoassay using an insulin radioimmunoassay bead kit (Dainabot, Tokyo, Japan).

2.1. Statistical analysis

Data are shown as mean ± SD. Significance ($P < .05$) was determined using analysis of variance.

3. Results

3.1. Experiment 1

3.1.1. Effects of sucrose on plasma concentrations of purine bases and uridine

Sucrose increased the plasma concentration of uric acid by 11% ($P < .01$) at periods 2 and 3 in experiment 1. In

Table 1
Effects of sucrose on plasma concentrations of purine bases and uridine

	Period 1	Period 2	Period 3
Hypoxanthine (μmol/L)	0.60 ± 0.11	0.76 ± 0.12	0.74 ± 0.25
Xanthine (μmol/L)	0.53 ± 0.16	0.57 ± 0.09	0.62 ± 0.22
Uric acid (μmol/L)	328 ± 60	364 ± 73*	363 ± 64*
Uridine (μmol/L)	4.68 ± 1.55	6.20 ± 1.91*	5.98 ± 1.92*

Values are expressed as mean ± SD.
* $P < .01$ as compared with the value at period 1.

Table 2
Effects of sucrose on urinary excretion of purine bases

	Period 1	Period 2	Period 3
Hypoxanthine (μmol/h)	2.88 ± 0.61	3.78 ± 0.46*	3.16 ± 0.41
Xanthine (μmol/h)	2.53 ± 1.06	2.40 ± 1.08	2.42 ± 1.08
Urate (μmol/h)	175 ± 32	163 ± 25	171 ± 28

Values are expressed as mean ± SD.
* $P < .05$ as compared with the values at period 1.

Table 3
Fractional excretion of hypoxanthine, xanthine, and uric acid and creatinine clearance

	Period 1	Period 2	Period 3
Hypoxanthine	72 ± 9	77 ± 14	69 ± 15
Xanthine	77 ± 42	65 ± 29	66 ± 33
Uric acid	8.1 ± 1.2	6.9 ± 1.2	7.4 ± 1.5
Ccr (mL/min)	109.3 ± 6.2	107.7 ± 8.0	107.4 ± 12.6

Values are expressed as mean ± SD. The fractional excretion of hypoxanthine, xanthine, and uric acid are expressed as percentage ratios of hypoxanthine clearance–creatinine clearance, xanthine clearance–creatinine clearance, and uric acid clearance–creatinine clearance, respectively. Ccr indicates creatinine clearance.

addition, that of uridine was increased by 32% ($P < .01$) at period 2 and 28% ($P < .01$) at period 3, whereas sucrose did not significantly increase the plasma concentration of hypoxanthine or xanthine (Table 1).

3.1.2. Effects of sucrose on urinary and fractional excretion of purine bases, and clearance of creatinine

Sucrose did not significantly affect the urinary excretion or fractional excretion of uric acid, hypoxanthine, and xanthine, except for a small increase in the urinary excretion of hypoxanthine at period 2. In addition, creatinine clearance did not change throughout the experiment (Tables 2 and 3).

3.1.3. Effects of sucrose on concentrations of glucose and insulin in plasma, and lactic acid in blood

The plasma concentration of glucose was increased by 38% ($P < .01$) at period 2 as compared with that at period 1, whereas the plasma concentration of insulin was also increased by 9.6-fold ($P < .01$) and 6.2-fold ($P < .01$) at periods 2 and 3, respectively (Table 4). In contrast, the serum concentration of potassium was decreased by 12% ($P < .05$) and 14% ($P < .01$) at periods 2 and 3, respectively, as compared with that at period 1. As for lactic acid, its blood concentration was increased by 2.6-fold ($P < .01$) and 2.5-fold ($P < .05$) at periods 2 and 3, respectively, as compared with that at period 1 (Table 4).

3.1.4. Effects of sucrose on serum concentration, urinary excretion, and fractional excretion of sodium

The serum concentration, urinary excretion, and fractional excretion of sodium did not significantly change throughout the experiment (Table 5).

Table 4
Effects of sucrose on concentrations of glucose and insulin in plasma, and lactic acid in blood, and potassium in serum

	Period 1	Period 2	Period 3
Glucose (mmol/L)	5.29 ± 0.46	7.27 ± 0.62**	5.60 ± 0.67
Lactic acid (mmol/L)	0.83 ± 0.32	2.19 ± 0.58**	2.08 ± 0.63*
Insulin (μU/mL)	7.6 ± 2.3	73.0 ± 19.8**	46.8 ± 7.0**
Potassium (mmol/L)	4.3 ± 0.4	3.8 ± 0.3*	3.7 ± 0.3**

Values are expressed as mean ± SD.
* $P < .05$ as compared with the value at period 1.
** $P < .01$ as compared with the value at period 1.

Table 5
Effects of sucrose on serum concentration, urinary excretion, and fractional excretion of sodium

	Period 1	Period 2	Period 3
Serum sodium (mmol/L)	141 ± 0	141 ± 2	142 ± 2
Urinary sodium (mmol/h)	6.6 ± 3.1	5.5 ± 1.3	5.7 ± 1.6
Fractional excretion of sodium	0.70 ± 0.32	0.59 ± 0.15	0.64 ± 0.23

Values are expressed as mean ± SD. The fractional excretion of sodium is expressed as the percentage ratio of sodium clearance–creatinine clearance.

3.2. Experiment 2

3.2.1. Effects of sucrose on plasma concentrations of purine bases and uridine after administration of allopurinol

The plasma concentrations of hypoxanthine and xanthine were increased by 2.4-fold ($P < .05$) and 1.2 -fold ($P < .05$), respectively, at period 2, and that of hypoxanthine was also increased by 1.8-fold ($P < .05$) at period 3 in experiment 2 (Table 6). In addition, the plasma concentration of uridine was increased by 32% ($P < .01$) and 34% ($P < .05$) at periods 2 and 3, respectively, as compared with that at period 1. In contrast, the plasma concentration of uric acid did not increase throughout the experiment (Table 6).

3.2.2. Effects of sucrose on urinary excretion and fractional excretion of purine bases after administration of allopurinol

The urinary excretion of hypoxanthine was increased by 3.42-fold ($P < .05$) and 2.8-fold ($P < .05$) at periods 2 and 3, respectively, as compared with that at period 1. In addition, the fractional excretion of hypoxanthine was increased by 1.6-fold ($P < .05$) and 1.6-fold ($P < .01$) at periods 2 and 3, respectively, whereas the urinary excretion of uric acid and xanthine, as well as creatinine clearance, and fractional excretion of uric acid and xanthine were not significantly changed throughout the experiment (Tables 7 and 8).

3.2.3. Plasma concentration and urinary excretion of oxypurinol

The plasma concentration and urinary excretion of oxypurinol were not changed throughout experiment 2 (plasma concentrations: 30.0 ± 9.2, 30.2 ± 9.6, and 29.6 ± 9.9 μmol/L at periods 1, 2, and 3, respectively; urinary excretion: 46.9 ± 14.3, 46.3 ± 12.6, and 50.6 ± 19.2 μmol/L at periods 1, 2, and 3, respectively).

Table 6
Effects of sucrose on plasma concentrations of purine bases and uridine after administration of allopurinol

	Period 1	Period 2	Period 3
Hypoxanthine (μmol/L)	1.79 ± 0.87	4.24 ± 1.86*	3.29 ± 2.15*
Xanthine (μmol/L)	4.86 ± 2.04	5.89 ± 2.06**	5.53 ± 2.47
Uric acid (μmol/L)	299 ± 74	298 ± 71	304 ± 64
Uridine (μmol/L)	4.04 ± 0.98	5.32 ± 0.96**	5.41 ± 1.26**

Values are expressed as mean ± SD.
* $P < .05$ as compared with the value at period 1.
** $P < .01$ as compared with the value at period 1.

Table 7
Effects of sucrose on urinary excretion of purine bases and creatinine clearance after administration of allopurinol

	Period 1	Period 2	Period 3
Hypoxanthine (μmol/h)	10.61 ± 5.21	36.32 ± 11.00**	29.43 ± 14.77*
Xanthine (μmol/L)	23.68 ± 8.50	27.64 ± 7.29	26.20 ± 6.27
Uric acid (μmol/L)	168 ± 45	144 ± 40	154 ± 42
Ccr (mL/min)	109.3 ± 11.4	105.2 ± 15.4	110.3 ± 13.1

Values are expressed as mean ± SD.
* $P < .05$ as compared with the value at period 1.
** $P < .01$ as compared with the value at period 1.

3.3. Experiment 3

The plasma concentrations of hypoxanthine, xanthine, uric acid, and uridine and the urinary excretion and fractional excretion of hypoxanthine, xanthine, and uric acid did not change throughout experiment 3 (data not shown). In addition, the plasma concentration and urinary excretion of oxypurinol were not changed (plasma concentrations: 27.5 ± 6.1, 27.2 ± 6.4, and 27.4 ± 6.4 μmol/L at periods 1, 2, and 3, respectively; urinary excretion: 38.1 ± 6.2, 36.1 ± 7.4, and 38.3.4 ± 7.9 μmol/L at periods 1, 2, and 3, respectively.)

4. Discussion

Fructose, a component of sucrose, is rapidly phosphorylated in the body using adenosine triphosphate (ATP). As a result, ATP is rapidly consumed, leading to adenine nucleotide degradation (ATP→adenosine diphosphate→adenosine monophosphate→inosine monophosphate→inosine→hypoxanthine→xanthine→uric acid) [4].

Previous studies [7,9] have demonstrated that sucrose intake increases serum urate levels, suggesting that fructose increases adenine nucleotide degradation, which also plays a role in increased serum uric acid. However, no conclusive evidence of sucrose-induced adenine nucleotide degradation has been presented. In the present study, we investigated the effects of sucrose on purine degradation using allopurinol because plasma oxypurines are reported to be sensitive markers of purine degradation in subjects treated with allopurinol [8,10]. In experiment 1, sucrose without the prior administration of allopurinol increased the plasma concentration of uric acid together with that of uridine, whereas it did not significantly affect the urinary excretion of uric acid or the plasma concentration and urinary excretion of oxypurines, except for a small increase in the urinary excretion of hypoxanthine at period 2 (Tables 1 and 2). Therefore, to confirm that an increase in plasma concentration of uric acid by sucrose is ascribable to enhanced purine degradation, we performed experiments 2 and 3 with an administration of allopurinol. In experiment 2, sucrose increased the plasma concentrations and urinary excretion of hypoxanthine and xanthine, together with the plasma concentration of uridine and the fractional excretion of hypoxanthine, whereas it did not significantly affect the plasma concentration and urinary excretion of uric acid (Tables 6-8). On the other hand, the plasma concentration and urinary excretion of purine bases and the plasma concentration of uridine did not change throughout experiment 3, during which sucrose was not administered (data not shown).

Oxypurinol is a metabolite of allopurinol and a potent inhibitor of xanthine dehydrogenase with a biological half-life longer than that of allopurinol, and the overall effect of allopurinol may be due to the action of oxypurinol [11]. In the presence of oxypurinol, the plasma concentration and urinary excretion of oxypurines are markedly increased by enhanced accelerated purine degradation, whereas those of uric acid are not. Because the plasma concentrations and urinary excretion of purine bases and oxypurinol did not significantly change throughout experiment 3 and the plasma concentration of oxypurinol did not change throughout experiment 2, the results in experiment 2 indicated that the increase in plasma concentration of uric acid caused by sucrose in experiment 1 was ascribable to enhanced purine degradation. In addition, the increase in plasma concentration of uridine together with sucrose-induced enhanced purine degradation strongly suggest that, after separation from sucrose by α-glucosidase, fructose accelerates adenine nucleotide degradation because plasma uridine is known to be increased by adenine nucleotide degradation by fructose (a component of sugar), ethanol, or exercise [12,13].

Glucose stimulates insulin secretion from islet beta cells, resulting in transient hyperinsulinemia. Exogenous insulin can reabsorb uric acid together with sodium in the renal tubules and decreases the urinary excretion of uric acid [14]. In addition, it is suspected that insulin may enhance renal urate reabsorption through stimulation of the urate-anion exchanger urate transporter 1 or through the sodium-dependent anion cotransporter in brush-border membranes of the renal proximal tubules [15]. Therefore, hyperinsulinemia may be a factor in hyperuricemia. In addition, glucose and fructose are partly metabolized to lactate, leading to an increase in its blood concentration, and lactate has been shown to inhibit the urinary excretion of uric acid [16]. Therefore, hyperinsulinemia and hyperlactatemia, due to excessive sucrose, lead to a decreased urinary excretion of uric acid. A previous study demonstrated that ingestion of a large amount of sucrose over a 2-week period decreased

Table 8
Effects of sucrose on fractional excretion of purine bases after administration of allopurinol

	Period 1	Period 2	Period 3
Hypoxanthine	92.1 ± 21.1	149.3 ± 68.8*	150.9 ± 51.6**
Xanthine	85.9 ± 37.4	81.3 ± 33.2	85.8 ± 47.6
Uric acid	8.5 ± 1.3	7.6 ± 0.7	7.5 ± 1.0

Values are expressed as mean ± SD. The fractional excretion of hypoxanthine, xanthine, and uric acid are expressed as percentage ratios of hypoxanthine clearance–creatinine clearance, xanthine clearance–creatinine clearance, and uric acid clearance–creatinine clearance, respectively.
* $P < .05$ as compared with the value at period 1.
** $P < .01$ as compared with the value at period 1.

the fractional excretion of uric acid [6]. However, the increase in blood concentration of lactic acid due to sucrose was not high enough to inhibit the urinary excretion of uric acid in the present study, which confirms the results of previous reports [8,16]. Furthermore, although sucrose increased insulin to an extent that serum potassium levels were decreased, the urinary excretion and fractional excretion of uric acid and sodium were not significantly decreased. These results suggest that hyperinsulinemia and hyperlactatemia caused by ingestion of sucrose at 1.5 g/kg of body weight were not adequate to inhibit the urinary excretion of uric acid during the experimental period.

In conclusion, the present results clearly demonstrated that sucrose enhances purine degradation, whereas it does not have an effect on the urinary and fractional excretion of uric acid and creatinine clearance. They also indicate that an increase in the plasma concentration of uric acid due to excessive sucrose intake is mainly ascribable to sucrose-induced purine degradation. A transient increase in insulin concentration in plasma and that of lactate in blood due to ingestion of sucrose at 1.5 g/kg of body weight may be not high enough to decrease the fractional excretion of uric acid. However, excessive sucrose intake causes obesity, which leads to hyperuricemia mainly via decreased urinary excretion of uric acid. Therefore, additional examinations are needed to elucidate the effects of long-term intake of large amounts of sucrose on the metabolism of uric acid.

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