Effect of Beer on the Plasma Concentrations of Uridine and Purine Bases

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We conducted the present study to determine whether beer, both with and without ethanol content, increases the plasma concentration and urinary excretion of purine bases and uridine. Because 10 mL of regular beer (with ethanol) was found to contain 0.34 g of freeze-dried beer (without ethanol) and 0.5 mg of uridine, 5 healthy males were given regular beer (10 mL/kg of body weight) and freeze-dried beer (0.34 g/kg of body weight) or uridine (0.5 mg/kg of body weight). The plasma concentrations of hypoxanthine, xanthine, and uridine increased by 3.5-fold ($P < .05$), 4.7-fold ($P < .05$), and 1.8-fold ($P < .05$), respectively, 30 minutes after regular beer ingestion, and the urinary excretion of hypoxanthine, xanthine, and uridine increased by 4.0-fold ($P < .05$), 4.5-fold ($P < .01$), and 1.7-fold ($P < .05$), respectively, when measured 1 hour after ingestion. The plasma concentrations of uric acid and total purine bases increased by 6.5% ($P < .05$) and 7.6% ($P < .05$), respectively, 30 minutes after regular beer ingestion, whereas the urinary excretion of uric acid did not increase, while that of total purine bases increased by 1.3-fold ($P < .05$) when measured 1 hour after ingestion. As for freeze-dried beer, the plasma concentrations of uric acid total purine bases increased by 4.4% ($P < .05$) and 4.6% ($P < .05$), respectively, and that of uridine by 1.5-fold ($P < .01$) 30 minutes after ingestion, while the urinary excretion of uridine increased by 1.4-fold ($P < .01$) 1 hour after ingestion. However, the plasma concentrations and urinary excretion of hypoxanthine and xanthine and the urinary excretion of uric acid and total purine bases did not change significantly. As for uridine ingestion, the plasma concentration of uridine increased by 1.37-fold ($P < .01$) 30 minutes after ingestion, and the urinary excretion of uridine increased by 1.3-fold ($P < .01$) 1 hour after ingestion. However, the plasma concentrations and urinary excretion of hypoxanthine, xanthine, uric acid, and total purine bases did not change significantly. These results suggest that the purines in beer played a major role in the increase in the plasma concentration of uric acid, while both uridine and ethanol in beer had a significant effect on the increase in plasma concentration of uridine.

ETHANOL IS KNOWN to have an effect on purine and pyrimidine metabolism.[1-3] With purine metabolism, the most important clinical effect of drinking alcoholic beverages is an increase in the plasma concentration of uric acid, and ingestion occasionally induces gouty arthritis in patients with gout. Several mechanisms of this ethanol-induced increase in plasma uric acid concentration have been reported.[3-5] First, an increase of lactic acid in blood from ethanol ingestion inhibits the urinary excretion of uric acid, resulting in an increase in its plasma concentration.[4] Second, adenosine triphosphate (ATP) consumption that is induced by ethanol ingestion causes purine degradation, resulting in accelerated uric acid production, which leads to an increase in the plasma concentration of uric acid.[5] Further, an increase in the plasma concentration of oxypurines (hypoxanthine and xanthine) from enhanced ATP consumption and slightly inhibited xanthine dehydrogenase activity come from ethanol metabolism.[6] Moreover, ethanol also increases the plasma concentration of uridine via enhanced ATP consumption.[1] Therefore, beer, as well as other alcoholic beverages, may increase the plasma concentrations of uric acid, oxypurines, and uridine. Beer has also been shown to increase the concentration of uric acid in serum[6] and is known to contain considerable amounts of purine (eg, guanosine, hypoxanthine, xanthine, and guanine) as compared with other alcoholic beverages. Purines are converted to uric acid in the body, thus, beer seems to cause a greater increase in the plasma concentration of uric acid than other alcoholic drinks. However, there is no known detailed study regarding the effect of beer without ethanol content on the plasma concentration and urinary excretion of purine bases. Further, there are no definitive data as to the content of uridine and its metabolites in beer or their effect on the plasma concentration of uridine, although beer seems to contain pyrimidines in addition to purines. Accordingly, we conducted the present study to investigate whether beer, with and without ethanol, and uridine have an effect on the plasma concentration and urinary excretion of uric acid, hypoxanthine, xanthine, and uridine.

SUBJECTS AND METHODS

Subjects

Five healthy males (age, 33 to 45 years; mean, 40 ± 6) were the subjects in the experiments and had normal values in a routine laboratory test (Table 1). The first study was performed as follows. After an overnight fast, except for water, the subjects completely voided their urine, and the first 1-hour urine samples were collected (first period). After the first urine samples were collected, regular beer (10 mL/kg body weight), containing 5% ethanol, was ingested orally within 5 minutes. The second urine samples were collected 1 hour (second period), the third urine samples were collected between 1 and 2 hours (third period), and the fourth urine samples were collected between 2 and 3 hours (fourth period) after beginning beer ingestion. The first, second, third, and fourth blood samples were drawn with heparinized syringes at the midpoint of the respective 1-hour urinary collections. Two weeks later, the second study was performed using the same protocol, with the administration of freeze-dried beer (0.34 g/kg body weight) reconstituted with water (10 mL/kg body weight) instead of

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Table 1. Subject Baseline Data

Subject No.	Age	Cr	ALT	AST	FBG	SBP/DPB	SUA	POx	UUa	UOx
1	33	0.98	22	18	95	125/73	348	1.08	162	4.93
2	45	1.12	24	22	101	133/81	370	1.45	213	5.29
3	45	1.08	27	20	93	115/71	357	1.68	217	7.62
4	41	1.03	23	21	103	135/82	346	1.63	150	4.93
5	33	0.95	28	23	98	120/74	382	1.21	172	2.93

Abbreviations: Cr, serum creatinine concentration (mg/dL); FBG, fasting blood glucose concentration (mg/dL); SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure; Sua, serum uric acid concentration (μmol/L); Pox, plasma oxypurine concentration (μmol/L); Uua, urinary uric acid excretion (μmol/h); Oox, urinary oxypurine excretion (μmol/h). Oxypurines denotes hypoxanthine + xanthine.

beer, because 10 mL of regular beer contains 0.34 g of content when freeze-dried. Four weeks later, the third study was performed using the same protocol by administering uridine (0.5 mg/kg body weight) instead of beer, because 10 mL of regular beer contains 0.5 mg uridine.

Reagents

Regular and freeze-dried beers were provided by Kirin Brewery, (Yokohama, Japan). Uric acid, hypoxanthine, xanthine, adenine, guanine, uracil, inosine, adenosine, guanosine, uridine, 2'-deoxyinosine, 2'-deoxyguanosine, 2'-deoxyadenosine, and 2'-deoxyuridine were purchased from Wako Pure Chemicals Industries (Osaka, Japan).

Blood and Urine Analyses

The concentrations of uridine, hypoxanthine, and xanthine in plasma and the concentrations of uridine, hypoxanthine, xanthine, inosine, adenosine, guanosine, deoxyinosine, deoxyguanosine, and deoxyadenosine in beer, as well as the concentrations of hypoxanthine and xanthine in urine were determined by high-performance liquid chromatography (HPLC), as previously described.[1] The concentrations of uridine in urine and adenine, guanine, deoxyuridine, and uracil in beer were determined by a modification of the previous HPLC method that used column switching.[1] In brief, the chromatograph consisted of 2 CCPM pumps (Tosoh, Tokyo, Japan), an SC-8020 system controller (Tosoh), 2 spectrophotometric detectors (UV-8010 and UV-8020) (Tosoh), and 2 VC-8020 column switching valves (Tosoh). The chromatographic columns were a Wakosil 5C18-200 (4.6X250 mm) (Wako Pure Chemicals) as the first column and a NAVI C18-5 (4.6X250 mm) (Wako Pure Chemicals) as the second column. In the first column, the mobile phase was 20 mmol/L KH_2PO_4 (pH 4.70) and in the second column, it was 20 mmol/L KH_2PO_4 (pH 2.20). The flow rate was 1 mL/min, and the detection wavelength was 254 nm. A total of 20 to 50 μL urine without dilution was applied onto the first column. At the fraction time in which uridine was eluted via the first column, the 2 columns were connected, and the eluate from the second column was monitored.

The plasma and urinary concentrations of uric acid were measured by the uricase method using an autoanalyzer. The concentrations of ethanol in plasma and lactic acid and pyruvic acid in blood were measured enzymatically, as described previously.[3]

Statistical Analysis

Values are shown as the mean ± SD. The significance of differences between means was analyzed by analysis of variance (ANOVA).

RESULTS

Effect of Regular Beer on the Plasma Concentrations of Purine Bases and Uridine

Regular beer ingestion increased the plasma concentrations of hypoxanthine, xanthine, and uridine by 3.5-fold ($P < .05$), 4.7-fold ($P < .05$), and 1.8-fold ($P < .01$), respectively, in the second period as compared with each reference value in the first period (Table 2). It also increased the plasma concentrations of hypoxanthine, xanthine, and uridine by 2.4-fold ($P < .05$), 4.1-fold ($P < .05$), and 1.7-fold ($P < .01$), respectively, in the third period and the plasma concentrations of xanthine and uridine by 3.1-fold ($P < .05$) and 1.7-fold ($P < .01$), respectively, in the fourth period (Table 2). Furthermore, it increased the plasma concentrations of uric acid and total purine bases by 6.5% ($P < .05$) and 7.6% ($P < .05$) in the second period, 9.6% ($P < .05$) and 10.1% ($P < .01$) in the third period, and 4.2% ($P < .05$) and 4.8% in the fourth period (Table 2).

Table 2. Effect of Regular Beer (with ethanol) on the Plasma Concentrations of Purine Bases and Uridine (N = 5)

	1st Period	2nd Period	3rd Period	4th Period
Hypoxanthine (μmol/L)	0.76 ± 0.36	2.65 ± 1.23*	1.81 ± 0.74*	1.44 ± 0.72
Xanthine (μmol/L)	0.63 ± 0.14	2.98 ± 1.82†	2.56 ± 1.62†	1.98 ± 0.88*
Uric acid (μmol/L)	355 ± 14	378 ± 17*	389 ± 10†	370 ± 12*
Total purine bases (μmol/L)	357 ± 13	384 ± 19*	393 ± 10†	374 ± 12*
Uridine (μmol/L)	3.78 ± 1.18	6.78 ± 1.32†	6.60 ± 0.71†	6.52 ± 0.97†

NOTE. Values are shown as the mean ± SD. After an overnight fast, except for water, the subjects completely voided their urine and the first 1-hour urine samples were collected (1st period). After the first urine samples were collected, regular beer (10 mL/kg body weight) was ingested orally within 5 minutes. The second urine samples were collected 1 hour (2nd period), the third urine samples were collected between 1 and 2 hours (3rd period), and the fourth urine samples were collected between 2 and 3 hours (4th period) after beginning beer ingestion. The first, second, third, and fourth blood samples were drawn with heparinized syringes at the midpoint of the respective 1-hour urinary collections.

*$P < .05$.

†$P < .01$.

Table 3. Effect of Regular Beer (with ethanol) on the Urinary Excretion of Purine Bases and Uridine (N = 5)

	1st Period	2nd Period	3rd Period	4th Period
Hypoxanthine (μmol/h)	2.44 ± 0.84	9.72 ± 3.68*	6.77 ± 1.15†	4.24 ± 1.18
Xanthine (μmol/h)	2.41 ± 0.78	10.94 ± 3.24†	11.22 ± 3.84†	9.21 ± 3.66*
Uric acid (μmol/h)	187 ± 29	230 ± 32	225 ± 39	223 ± 36
Total purine bases (μmol/h)	192 ± 30	250 ± 35*	243 ± 42	236 ± 35
Uridine (μmol/h)	0.083 ± 0.023	0.144 ± 0.055*	0.133 ± 0.053*	0.144 ± 0.043*

NOTE. Values are shown as the mean ± SD.
*$P < .05$.
†$P < .01$.

Effect of Regular Beer on the Urinary Excretion of Purine Bases and Uridine

Regular beer ingestion increased the urinary excretion of hypoxanthine, xanthine, total purine bases, and uridine by 4.0-fold ($P < .05$), 4.5-fold ($P < .01$), 1.3-fold ($P < .05$), and 1.7-fold ($P < .05$), respectively, in the second period as compared with each reference value in the first period (Table 3). It also increased the urinary excretion of hypoxanthine, xanthine, and uridine by 2.8-fold ($P < .01$), 4.7-fold ($P < .01$), and 1.6-fold ($P < .05$), respectively, in the third period and that of xanthine and uridine by 3.8-fold ($P < .01$) and 1.7-fold ($P < .05$), respectively, in the fourth period (Table 3). On the other hand, it did not significantly increase the urinary excretion of uric acid during the study (Table 3).

Effect of Freeze-Dried Beer on the Plasma Concentrations of Purine Bases and Uridine

Freeze-dried beer content ingestion increased the plasma concentrations of uric acid and total purine bases by 4.4% ($P < .05$) and 4.6% ($P < .05$), respectively, in the second period, by 5.7% ($P < .05$) and 5.7% ($P < .05$), respectively, in the third period, and by 3.3% ($P < .05$) and 3.3%, respectively, in the fourth period as compared with the reference values in the first period (Table 4). It also increased the plasma concentration of uridine by 1.5-fold ($P < .01$), 1.3-fold ($P < .01$), and 1.3-fold ($P < .01$) in the second, third, and fourth periods, respectively (Table 4). On the other hand, it did not significantly increase the plasma concentrations of hypoxanthine and xanthine at any time during the study (Table 4).

Effect of Freeze-Dried Beer on the Urinary Excretion of Purine Bases and Uridine

Freeze-dried beer content ingestion increased the urinary excretion of uridine by 1.5-fold ($P < .01$), 1.4-fold ($P < .01$), and 1.2-fold ($P < .01$) in the second, third, and fourth periods, respectively, as compared with the reference value in the first period (Table 5). On the other hand, it did not significantly increase the urinary excretion of hypoxanthine, xanthine, uric acid, or total purine bases at any time during the study (Table 5).

Concentrations of Lactic Acid and Pyruvic Acid in Blood After Regular Beer and Freeze-Dried Beer Ingestion

Regular beer ingestion increased the concentration of lactic acid in blood by 49% ($P < .01$), 53% ($P < .01$), and 55% ($P < .01$) in the second, third, and fourth periods, respectively, as compared with the reference value in the first period (Table 6). In contrast, the concentration of pyruvic acid in blood was decreased by 60% ($P < .05$), 57% ($P < .01$), and 57% ($P < .05$) in the same periods (Table 6). However, freeze-dried beer content ingestion did not affect the concentrations of lactic acid or pyruvic acid in blood at any time during the study (Table 6).

Plasma Concentration of Ethanol in Blood After Regular Beer and Freeze-Dried Beer Ingestion

The plasma concentration of ethanol was below the limits of detection, 518 ± 23, 414 ± 74, and 276 ± 59 g/mL in the first, second, third, and fourth periods, respectively, in the beer ingestion study, while it was below the limits of detection during the freeze-dried beer content ingestion study.

Purine and Pyrimidine in Beer

Beer was found to contain many kinds of purine nucleosides and purine bases, which were considered to contribute to an increase in the plasma concentration of uric acid. Among them, the concentration of guanosine was highest (Table 7). Beer also

Table 4. Effect of Freeze-Dried Beer (without ethanol) on the Plasma Concentration of Purine Bases and Uridine (N = 5)

	1st Period	2nd Period	3rd Period	4th Period
Hypoxanthine (μmol/L)	0.88 ± 0.23	1.09 ± 0.32	0.97 ± 0.22	0.87 ± 0.17
Xanthine (μmol/L)	0.58 ± 0.22	0.74 ± 0.22	0.71 ± 0.27	0.62 ± 0.15
Uric acid (μmol/L)	366 ± 23	382 ± 31*	387 ± 24*	378 ± 21*
Total purine bases (μmol/L)	367 ± 23	384 ± 31*	388 ± 24*	379 ± 20*
Uridine (μmol/L)	3.72 ± 1.03	5.41 ± 1.11†	4.94 ± 1.12†	4.73 ± 1.29*

NOTE. Values are shown as the mean ± SD. The study was performed using the same protocol as in Table 2, with the administration of freeze-dried beer instead of beer.
*$P < .05$.
†$P < .01$.

Table 5. Effect of Freeze-Dried Beer (without ethanol) on the Urinary Excretion of Purine Bases and Uridine (N = 5)

	1st Period	2nd Period	3rd Period	4th Period
Hypoxanthine (μmol/h)	2.50 ± 1.19	3.47 ± 1.15	3.27 ± 1.03	2.77 ± 0.64
Xanthine (μmol/h)	2.16 ± 0.55	3.10 ± 0.84	2.68 ± 0.5	2.74 ± 0.46
Uric acid (μmol/h)	187 ± 35	180 ± 29	172 ± 28	187 ± 44
Total purine bases (μmol/h)	191 ± 36	187 ± 30	178 ± 27	193 ± 43
Uridine (μmol/h)	0.073 ± 0.015	0.112 ± 0.024*	0.102 ± 0.017*	0.086 ± 0.015*

NOTE. Values are shown as the mean ± SD.
*$P < .01$.

had a considerable amount of uridine, which may have contributed to the increase in its plasma concentration seen in the present subjects (Table 7).

Effect of Uridine on the Plasma Concentrations and Urinary Excretion of Uridine and Purine Bases

Uridine ingestion increased its plasma concentration from 4.13 ± 0.35 mol/L in the first period to 5.65 ± 0.76 ($P < .01$), 5.10 ± 0.64 ($P < .01$), and 4.96 ± 0.56 ($P < .01$) mol/L in the second, third, and fourth periods, respectively (Table 8). It also increased the urinary excretion of uridine from 0.073 ± 0.015 mol/h in the first period to 0.095 ± 0.023 ($P < .01$), 0.0930 ± 0.023 ($P < .01$), and 0.088 ± 0.017 ($P < .01$) mol/h in the second, third, and fourth periods, respectively (Table 9). On the other hand, the plasma concentrations and urinary excretion of hypoxanthine, xanthine, uric acid, and total purine bases were not affected (Tables 8 and 9).

Comparison of the Plasma Concentration and Urinary Excretion of Total Purine Bases Among Beer, Freeze-Dried Beer, and Uridine

The plasma concentrations of total purine bases after ingesting regular beer and freeze-dried beer were increased by 7.3% ($P < .05$) and 7.3% ($P < .05$), respectively, in the second period, by 9.4% ($P < .01$) and 8.1% ($P < .05$), respectively, in the third period, and by 4.5% ($P < .05$) and 5.7% ($P < .01$), respectively, in the fourth period as compared with each value at the respective periods after taking uridine (Fig 1). Further, the urinary excretion of total purine bases after drinking beer was increased by 1.5-fold ($P < .05$) and by 1.3-fold ($P < .05$), respectively, in the second period as compared with each value after ingesting freeze-dried beer and uridine ($P < .05$) (Fig 1).

DISCUSSION

The results of the present study found that beer, both regular and freeze-dried (without ethanol), increased the plasma concentrations of uric acid and uridine without a decrease in the urinary excretion of uric acid or uridine (Tables 2 through 5), indicating that some contents other than ethanol contribute to increases in the plasma concentrations of uric acid and uridine that accompany regular beer ingestion. Further, regular beer was found to contain uridine and many kinds of purines (Table 7). We also showed that uridine ingestion increased the plasma concentration of uridine. These results together indicate that the purines and uridine contained in beer contribute to an increase in the plasma concentrations of uric acid and uridine, respectively, that accompany regular beer ingestion.

In the present healthy subjects, freeze-dried beer did not have an effect on the plasma concentration and urinary excretion of oxypurines (Tables 4 and 5), although the plasma concentration of uric acid was increased. This finding suggests that purines are rapidly converted to uric acid via xanthine in the intestine and liver before entering the hepatic veins, because purine nucleoside phosphorylase, converting nucleosides (guanosine and inosine) to purine bases (guanine and hypoxanthine), xanthine dehydrogenase, converting hypoxanthine and xanthine to uric acid, and guanine deaminase, converting guanine to xanthine, are abundant in these organs.

In a previous study,[2] ethanol at 0.8 mL/kg body weight (0.63 g) increased the plasma concentration of oxypurines, especially xanthine, but did not affect that of uric acid. In the present

Table 6. Effect of Regular and Freeze-Dried Beer on the Concentrations of Lactic Acid and Pyruvic Acid in Blood (N = 5)

	1st Period	2nd Period	3rd Period	4th Period
Regular beer				
Lactic acid (mmol/L)	1.03 ± 0.18	1.53 ± 0.19*	1.58 ± 0.11*	1.60 ± 0.17*
Pyruvic acid (mmol/L)	0.070 ± 0.015	0.028 ± 0.008†	0.030 ± 0.006*	0.030 ± 0.010†
Freeze-dried beer				
Lactic acid (mmol/L)	1.20 ± 0.0.21	1.23 ± 0.0.27	1.32 ± 0.35	1.26 ± 0.0.27
Pyruvic acid (mmol/L)	0.076 ± 0.014	0.081 ± 0.017	0.078 ± 0.019	0.070 ± 0.016

NOTE. Values are shown as the mean ± SD.
*$P < .01$.
†$P < .05$.

Table 7. Concentrations of Purine-Nucleosides and Bases and Uridine and its Metabolites in Beer (μmol/L) (N = 3)

Hypoxanthine	17.5 ± 1.5
Xanthine	58.5 ± 3.6
Guanine	42.4 ± 3.6
Adenine	17.2 ± 2.3
Uric acid	ND
Uracil	17.6 ± 1.5
Inosine	20.3 ± 2.5
Guanosine	174 ± 16.1
Adenosine	42.1 ± 7.9
Uridine	210.6 ± 27.2
2′-Deoxyguanosine	ND
2′-Deoxyadenosine	19.4 ± 3.7
2′-Deoxyinosine	ND
2′-Deoxyuridine	7.9 ± 2.1

NOTE. Values are shown as the mean ± SD.
Abbreviation: ND, not detected.

study, regular beer, which contains ethanol (0.5 g/kg body weight), increased the plasma concentrations of both uric acid and oxypurines, while freeze-dried beer increased the plasma concentration of uric acid, but had no effect on that of oxypurines. In addition, neither type of beer inhibited the urinary excretion of uric acid, although the concentration of lactic acid in blood, which may affect the renal excretion of uric acid, was increased by regular beer (Table 6). Further, the increase in plasma concentration of uric acid by regular beer ingestion was not different from that by freeze-dried beer. Therefore, although the urinary excretion of total purine bases was increased by beer, the increase in plasma concentration of uric acid by beer is ascribable to beer contents rather than ethanol.

Ethanol is known to accelerate ATP consumption via ethanol metabolism, resulting in purine degradation (ATP→ADP→AMP→inosine→hypoxanthine→xanthine→uric acid).[1-3,5] In addition, ethanol converts oxidized nicotinamide adenine dinucleotide (NAD) to reduced nicotinamide adenine dinucleotide (NADH) via the oxidation of ethanol (acetic acid via acetaldehyde) in the liver, decreasing the ratio of NAD/NADH.[1,2] An increase in the blood lactic acid/pyruvic acid ratio, as shown in the present study, reflects a decrease in the ratio of NAD/NADH in cytosol, suggesting an increase in the concentration of NADH in the cytosol of liver cells. NADH increased by ethanol may slightly inhibit xanthine dehydrogenase activity in cytosol, leading to an increase in the plasma concentration of oxypurines. Ethanol-induced purine degradation and xanthine dehydrogenase inhibition, along with the purine degradation caused by beer, may together enhance an increase in the plasma concentration of oxypurines, as ethanol ingestion together with inosine intake has previously been shown to do.[2] Accordingly, the marked increase in plasma concentration of oxypurines by regular beer, which contains both purines and ethanol, in the present study suggests that the marked increase in plasma concentration of oxypurines after regular beer ingestion is ascribable to ethanol and enhanced by purines. Further, the increase in plasma concentration of total purine bases by beer was not different from that by freeze-dried beer; whereas the urinary excretion of total purine bases was increased by beer in comparison to freeze-dried (Fig 1), suggesting that the ethanol content accelerated ATP consumption and then enhanced purine degradation.

In our recent report,[7] inosine (20 mg/kg body weight) increased the plasma concentration and urinary excretion of uridine, presumably via a competitive inhibition of uridine uptake by inosine, because inosine, guanosine, and uridine are each transported via the nucleoside transport pathway of the small intestine and liver cells. However, neither guanosine (0.5 mg/kg body weight) nor inosine (0.5 mg/kg body weight) ingestion increased the plasma concentration of uridine (unpublished data). In contrast, in the present study, uridine (0.5 mg/kg body weight) ingestion increased the plasma concentration of uridine, suggesting that uridine phosphorylase and uridine kinase in the intestine and liver are not abundant enough to completely convert uridine to uracil and uridine 5′-monophosphate (UMP), respectively, before entering the hepatic vein. Therefore, the increase in plasma concentration of uridine by freeze-dried beer seems to be mainly ascribable to the uridine content, although purine nucleosides (inosine, adenosine, and guanosine) may also play a minor role via their competitive inhibition of uridine uptake.

Ethanol has been shown to increase the plasma concentration of uridine presumably via an abrupt consumption of ATP, as do fructose, xylitol, muscular exercise, and ischemia.[1,8-12] Because uridine diphosphate (UDP) is phosphorylated into uridine triphosphate (UTP) using ATP, a decrease in the concentration of ATP leads to an increase in the concentrations of UDP and UMP, resulting in an accelerated conversion of UMP to uridine. As a result, uridine is leaked into the blood, and its plasma level increases. In our subjects, the uridine in freeze-dried beer increased its plasma concentration, as did the ingestion of

Table 8. Effect of Uridine on the Plasma Concentration of Purine Bases and Uridine (N = 5)

	1st Period	2nd Period	3rd Period	4th Period
Hypoxanthine (μmol/L)	0.64 ± 0.16	0.69 ± 0.20	0.61 ± 0.17	0.58 ± 0.10
Xanthine (μmol/L)	0.58 ± 0.10	0.60 ± 0.08	0.61 ± 0.14	0.62 ± 0.12
Uric acid (μmol/L)	358 ± 16	357 ± 15	359 ± 16	359 ± 16
Total purine bases (μmol/L)	359 ± 16	358 ± 15	359 ± 16	358 ± 15
Uridine (μmol/L)	4.13 ± 0.35	5.65 ± 0.76*	5.10 ± 0.64*	4.96 ± 0.56*

NOTE. Values are shown as the mean ± SD. The study was performed using the same protocol as in Table 2, with the administration of freeze-dried beer instead of beer.
*$P < .01$.

Table 9. Effect of Uridine on the Urinary Excretion of Purine Bases and Uridine (N = 5)

	1st Period	2nd Period	3rd Period	4th Period
Hypoxanthine (μmol/h)	3.09 ± 0.92	2.97 ± 0.92	3.17 ± 1.01	2.94 ± 1.11
Xanthine (μmol/h)	2.83 ± 1.30	2.60 ± 0.65	2.85 ± 1.04	2.49 ± 0.65
Uric acid (μmol/h)	175 ± 32	166 ± 28	177 ± 29	173 ± 35
Total purine bases (μmol/h)	181 ± 32	172 ± 27	183 ± 29	179 ± 34
Uridine (μmol/h)	0.073 ± 0.015	0.095 ± 0.023*	0.093 ± 0.023*	0.088 ± 0.017*

NOTE. Values are shown as the mean ± SD.
*$P < .01$.

uridine. Therefore, an increase in the plasma concentration of uridine accompanied by regular beer ingestion is likely ascribable to both ethanol and uridine in its contents.

The present finding regarding the effect of beer on purine metabolism is clinically important, because an increase in the plasma concentrations of purine bases (hypoxanthine, xanthine, and uric acid) after regular beer ingestion may induce gouty arthritis in patients with gout. Therefore, drinking large amounts of beer is not recommended for these patients or those with asymptomatic hyperuricemia, as ingesting large amounts of purine-rich food is known to be risky. However, because the present results came from 4-hour experiments, a long-term study would be needed to elucidate the expected changes in plasma uric acid concentration associated with beer ingestion.

Beer markedly increased the plasma concentration of uridine. However, its physiologic role in plasma remains undetermined. Uridine (a pyrimidine nucleoside) is known to be an essential substance for the synthesis of RNA and is transported in plasma into cells via nucleoside transport pathways for the endogenous synthesis of nucleic acids. In addition to nucleic biosynthesis, uridine may have other physiologic actions, because its plasma level is considerably higher than other purine and pyrimidine nucleosides in humans. In a previous report,[13] it was shown that uridine had a vasoconstrictive effect in rats, which was reduced by adenosine. In another study,[14] it was shown that plasma uridine levels in deoxycorticosterone (DOCA)-salt hypertensive rats were reduced when compared with control rats, indicating that the metabolic clearance of uridine in test rats was increased and that uridine may be associated with vasoconstriction. However, because the physiologic action of plasma uridine in humans remains undetermined, further investigation is needed.

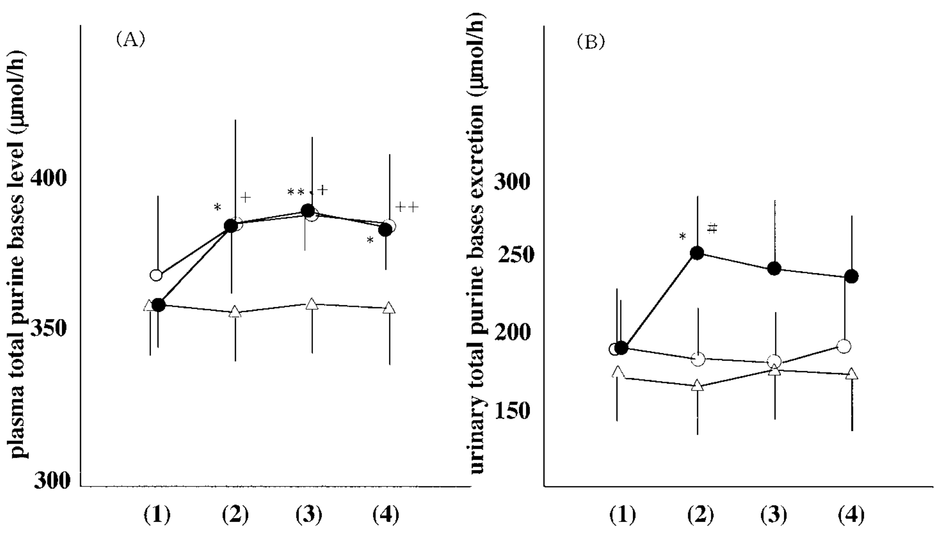

Fig 1. Effect of ingestion of beer (●), freeze-dried beer (○), and uridine (◁) on (A) plasma concentration (n = 5) and (B) urinary excretion of total purine bases (hypoxanthine, xanthine, and uric acid) (n = 5). (1) First period; (2) second period; (3) third period; (4) fourth period; vertical bar, SD; *$P < .05$ and **$P < .01$ in the same period between beer ingestion and uridine ingestion; $^{+}P < .05$ and $^{++}P < .01$ in the same period between freeze-dried beer ingestion and uridine ingestion; $^{\#}P < .05$ in the same period between beer ingestion and freeze-dried beer ingestion.

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