# Effect of Inosine on the Plasma Concentration of Uridine and Purine Bases

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**To examine whether inosine increases the plasma concentration of uridine, 20 mg/kg body weight of inosine was orally administered to 5 healthy subjects. The plasma concentration of uridine was increased by 1.25-fold ($P < .05$), while that of hypoxanthine, xanthine, and uric acid was increased by 1.26-fold ($P < .01$), 1.26-fold ($P < .01$), and 1.2-fold ($P < .05$), respectively, 2.5 hours after the oral administration of inosine. In addition, the 1-hour urinary excretion of uridine was increased by 1.17-fold ($P < .05$) and that of hypoxanthine, xanthine, and uric acid by 1.38-fold ($P < .05$), 1.4-fold ($P < .05$), and 1.4-fold ($P < .05$) between 2 and 3 hours after the administration of inosine. We also conducted an in vitro study with Mahlavu cells and found that the addition of inosine (50 μmol/L) inhibited a decrease in the concentration of uridine in medium originally containing 50 μmol/L uridine. Further, we demonstrated that the apparent Km and Vmax values for Na-independent uridine transport were 67.0 ± 4.3 μmol/L and 7.0 ± 0.3 pmol/mg protein/s, respectively, and the Ki value of inosine for Na-independent uridine transport was 45.1 ± 12.1 μmol/L. These results suggest that inosine inhibits uridine uptake via the nucleoside transport pathway, and administered inosine is converted to purine bases (uric acid, hypoxanthine, and xanthine) in the intestine and liver, before entering the systemic circulation via the hepatic vein.**


URIDINE IS A pyrimidine nucleoside that forms a part of RNA which is not only necessary for the endogenous synthesis of nucleic acids[1,2] but also plays an important role in the synthesis of glycogen. In humans, uridine is present in body fluids, such as blood and cerebrospinal fluid. Recent studies[3-6] have demonstrated that the plasma concentration of uridine is increased by ethanol ingestion, fructose infusion, xylitol infusion, and muscle exercise, suggesting that abrupt adenosine triphosphate (ATP) consumption induces pyrimidine degradation (uridine triphosphate [UTP]→uridine diphosphate [UDP]→uridine monophosphate [UMP]→uridine). Further, another report[7] showed that the plasma concentration of uridine was also increased by an oral administration of glucose, suggesting that glucose ingestion accelerates an abrupt release of UDP from UDP-glucose in parallel with the enhancement of glycogen synthesis, leading to pyrimidine degradation (UDP→UMP→uridine). In contrast, others[8-10] have demonstrated that the plasma concentration of uridine was decreased by infusion of either glucagon, dibutyric cyclic adenosine monophosphate (AMP), or amino acid, suggesting that these substances enhance uridine uptake into cells via the nucleoside transport pathway, leading to a decrease in the plasma concentration of uridine. Therefore, it is suggested that the plasma concentration of uridine may depend on uridine transport as well as pyrimidine degradation.

The Na-dependent transport of nucleosides including uridine is enhanced in response to a mitogenic stimulus, as in a partial hepatectomy[2]; therefore, the physiological role of the Na-dependent nucleoside transport pathway is to preserve extracellular nucleoside for the endogenous synthesis of nucleic acids.[1,2] As a result, uridine, which occupies a large part of the nucleosides present in plasma, may play a role clinically in nucleic biosynthesis in a physiological situation. The transport of uridine into or out of cells depends on nucleoside transport pathways, which are shared by both purine and pyrimidine nucleosides. Recently, an in vitro study[11] demonstrated that uridine uptake into cancer cells (lung cancer cell line A549) was inhibited competitively by inosine, strongly suggesting that the plasma concentration of uridine is related to uridine uptake into cells via the nucleoside transport pathway. We administered inosine orally and examined whether the plasma uridine level increased, since the human small intestine and liver possess nucleoside transport pathways. In addition, we measured the plasma concentrations of oxypurines together with purine bases before and after oral administration of inosine to determine the amount of increase of the plasma concentrations of oxypurines caused by administration of inosine, as there are few known previous studies on the effect of inosine ingestion on oxypurines in humans. Further, we investigated the effect of inosine on uridine transport in a hepatoma cell line, Mahlavu, in vitro.

## MATERIALS AND METHODS

### *Chemicals*

Uridine, hypoxanthine, xanthine, and uric acid were purchased from Sigma Chemical (St Louis, MO). Inosine was purchased from Morishita Rucel (Osaka, Japan). Other chemicals were obtained from Wako Pure Chemicals (Osaka, Japan).

### *Subjects and Protocol*

After informed consent was obtained, we conducted the first experiment on 5 healthy subjects aged 32 to 50 years. After an overnight fast except for water, 1-hour urine was collected 4 times over 4 hours and blood was drawn at the mid point of each urinary collection. Subjects received inosine (20 mg/kg body weight) after the first 1-hour urinary collection. Two weeks later, the control study was performed in which the protocol was the same without the administration of inosine.

### *Incubation Studies of Hepatoma-Derived Cell Line (Mahlavu)*

Cells from Mahlavu, a hepatoma cell line, were propagated in minimum Eagle's medium (MEM) supplemented with 10% fetal calf

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serum (FCS), 100 IU/mL penicillin, and 100 μg/mL kanamycin in a humidified atmosphere of 5% $CO_2$ in air, and then subcultured at a 1:5 dilution every 3 days. Inocula of $5 \times 10^5$ cells were seeded into 2-$cm^2$ wells on 24-well plates (Iwaki Glass, Chiba, Japan) with 1 ml of the medium described above. After an overnight culture, the conditioned medium was aspirated, the cells were rinsed 3 times with serum-free fresh medium, and then 1 mL of fresh medium containing uridine was added with or without inosine. Thirty and 60 minutes after replacement of fresh medium, 50 μL of the medium supernatant was aspirated. These experiments were performed in duplicate 3 times.

### *Transport Studies of Uridine in Mahlavu Cells*

A uridine transport study was performed as described previously.[11] In brief, Mahlavu cells were propagated as described above. After an overnight culture, the conditioned medium was aspirated and the wells were rinsed 3 times with 1.0 mL of medium containing 145 mmol/L KCl, 4.2 mmol/L $KHCO_3$, 0.36 mmol/L $K_2HPO_4$, 1.3 mmol/L $CaCl_2.2H_2O$, 0.44 mmol/L $KH_2PO_4$, 0.5 mmol/L$MgCl_2.6H_2O$, and 10 mmol/L HEPES (*P* H 7.4). The uptake of uridine was initiated by the addition of 0.2 mL of the above medium with the following substitutions: 140 mmol/LNaCl, 4.2 mmol/L $NaHCO_3$ and 5 mmol/L KCl substituted for 145 mmol/LKCl and 4.2 mmol/L $KHCO_3$ for analysis of the Na-dependent + Na-independent transport or 140 mmol/L *N*-methyl-D-glucamine (HCl) and 5 mmol/L KCl (Na-free medium) substituted for 145 mmol/L KCl and 4.2 mmol/L $KHCO_3$ for analysis of the Na-independent transport[4]). The transport medium contained [$^3$H] uridine (10 μCi/mL), inulin [$^{14}$C]carboxylic acid (0.4 μCi), and various concentrations of uridine with 50 μmol/L of inosine. After an appropriate interval, the transport was terminated by aspirating the medium and washing the cells 3 times with 1.0-mL aliquots of ice-cold Na-free medium (total time 10 seconds). Cells were lysed by the addition of 0.2 mL of 0.5 mol/L NaOH and assayed for radioactivity. The results of these uptake experiments, corrected for adhering extracellular medium using inulin [$^{14}$C]carboxylic acid, an extracellular marker, are expressed per milligram of protein.

### *Blood and Urine Analyses*

Plasma concentrations of uridine, hypoxanthine, and xanthine were determined by high-performance liquid chromatography (HPLC) as described previously,[12] as were the urinary concentrations of hypoxanthine and xanthine.[13] The urinary concentration of uridine was also determined by HPLC with column switching.[13] In brief, the chromatograph consisted of 2 CCPM pumps (Tosoh, Tokyo, Japan), an SC-8020 system controller (Tosoh), and 2 spectrophotometric detectors (UV-8010 and UV-8020; Tosoh) with VC-8020 column switching valves (Tosoh). The chromatographic columns used were a Wakosil 5C18-200 (4.6 × 250 mm; Wako Pure Chemicals) as the first column and a Tosoh TSK Gel (ODS-120A; 4.6 × 250 mm) as the second column. In both, the mobile phase was 20 mmol/L $KH_2PO_4$ (pH 2.2), the flow rate was 1 mL/min, and the detection wavelength was 254 nm. Twenty microliters of 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 elute was monitored from the second column. The plasma concentration and urinary concentration of uric acid were then measured using the uricase method with an autoanalyzer. Concentrations of oxypurines, uracil, inosine, and uridine in the conditioned medium were also measured using HPLC as described above. The percentage ratios of uric acid clearance/creatinine clearance (fractional uric acid clearance), hypoxanthine clearance/creatinine clearance (fractional hypoxanthine clearance), xanthine clearance/creatinine clearance (fractional xanthine clearance), and uridine clearance/creatinine clearance (fractional uridine clearance) were calculated.

### *Statistical Analysis*

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

## RESULTS

### *Effect of Inosine on the Plasma Concentrations of Purine Bases and Uridine*

Inosine intake increased the plasma concentration of hypoxanthine by 1.26-fold in the fourth period ($P < .01$), as compared with the reference value (the first period), and it also increased that of xanthine by 1.23-fold in the third period ($P < .01$) and by 1.26-fold in the fourth period ($P < .01$) (Table 1). In addition, inosine increased the plasma concentration of uric acid by 1.2-fold at the third period ($P < .05$) and by 1.2-fold in the fourth period ($P < .05$), as compared with the reference value (the first period), and increased that of uridine by 1.25-fold in the fourth period ($P < .05$) (Table 1). However, the plasma concentration of inosine did not change significantly after the intake of inosine, suggesting that inosine is converted to purine bases before entering the systemic circulation. In the control study, there were no significant changes in the plasma concentrations of purine bases or uridine (Table 1).

**Table 1. Effect of Inosine on the Plasma Concentrations of Purine Bases and Uridine (n = 5)**

| | First Period | Second Period | Third Period | Fourth Period |
|---|---|---|---|---|
| Inosine ingestion | | | | |
| Hypoxanthine (μmol/L) | 0.78 ± 0.12 | 0.82 ± 0.13 | 0.90 ± 0.05 | 0.98 ± 0.09† |
| Xanthine (μmol/L) | 0.70 ± 0.07 | 0.74 ± 0.09 | 0.86 ± 0.10† | 0.88 ± 0.10† |
| Uric acid (μmol/L) | 345 ± 30 | 369 ± 38 | 400 ± 43* | 417 ± 48* |
| Uridine (μmol/L) | 4.40 ± 0.64 | 4.58 ± 0.58 | 4.94 ± 0.56 | 5.48 ± 0.54* |
| Inosine (μmol/L) | 0.10 ± 0.02 | 0.11 ± 0.04 | 0.12 ± 0.04 | 0.12 ± 0.03 |
| Control | | | | |
| Hypoxanthine (μmol/L) | 0.72 ± 0.13 | 0.72 ± 0.10 | 0.72 ± 0.10 | 0.74 ± 0.07 |
| Xanthine (μmol/L) | 0.70 ± 0.07 | 0.68 ± 0.07 | 0.68 ± 0.07 | 0.70 ± 0.07 |
| Uric acid (μmol/L) | 345 ± 25 | 339 ± 23 | 345 ± 21 | 339 ± 23 |
| Uridine (μmol/L) | 4.48 ± 0.60 | 4.46 ± 0.56 | 4.46 ± 0.56 | 4.46 ± 0.56 |
| Inosine (μmol/L) | 0.094 ± 0.011 | 0.099 ± 0.017 | 0.096 ± 0.015 | 0.097 ± 0.015 |

NOTE. Values are expressed as mean ± SD. First period: 1-hour period before the administration of inosine (20 mg/kg body weight); second period: 1-hour period after the administration of inosine; third period: 1-hour period from 1 to 2 hours after the administration of inosine; fourth period: 1-hour period from 2 to 3 hours after the administration of inosine. Blood was drawn at the mid-point of each period.

*$P < .05$ and †$P < .01$, *v* respective value in the first period.

**Table 2. Effect of Inosine on the Urinary Excretion of Purine Bases and Uridine (n = 5)**

| | First Period | Second Period | Third Period | Fourth Period |
|---|---|---|---|---|
| Inosine ingestion | | | | |
| Hypoxanthine (μmol/h) | 3.48 ± 0.87 | 3.56 ± 0.85 | 4.75 ± 0.92* | 4.80 ± 0.82* |
| Xanthine (μmol/h) | 2.69 ± 0.52 | 2.76 ± 0.38 | 3.31 ± 0.93* | 3.76 ± 0.98* |
| Uric acid (μmol/h) | 180 ± 33 | 214 ± 40 | 239 ± 44 | 254 ± 63* |
| Uridine (μmol/h) | 0.093 ± 0.009 | 0.097 ± 0.008 | 0.101 ± 0.011 | 0.109 ± 0.016* |
| Control | | | | |
| Hypoxanthine (μmol/h) | 3.46 ± 0.66 | 3.48 ± 0.76 | 3.47 ± 0.75 | 3.32 ± 0.72 |
| Xanthine (μmol/h) | 2.72 ± 0.49 | 2.66 ± 0.49 | 2.70 ± 0.56 | 2.73 ± 0.52 |
| Uric acid (μmol/h) | 182 ± 29 | 176 ± 33 | 181 ± 23 | 183 ± 28 |
| Uridine (μmol/h) | 0.092 ± 0.007 | 0.092 ± 0.006 | 0.090 ± 0.007 | 0.091 ± 0.006 |

NOTE. Values are expressed as mean ± SD. First, second, third, and fourth periods are the same as described in Table 1.
*$P < .05$ *v* respective value in the first period.

*Effect of Inosine Intake on the Urinary Excretion of Purine Bases and Uridine*

Inosine intake increased the urinary excretion of hypoxanthine by 1.36-fold in the third period ($P < .05$) and by 1.38-fold in the fourth period ($P < .05$), as compared with the reference value (the first period), and it also increased the urinary excretion of xanthine by 1.4-fold in the fourth period ($P < .05$). In addition, inosine intake increased the urinary excretion of uric acid by 1.4-fold in the fourth period ($P < .05$), as compared with the reference value (the first period), and that of uridine by 1.17-fold in the fourth period ($P < .05$) (Table 2). In the control study, there were no significant changes in the urinary excretion of purine bases or uridine (Table 2).

*Effect of Inosine Intake on the Fractional Clearance of Purine Bases and Uridine, and the Clearance of Creatinine*

There were no significant changes in the fractional clearance of hypoxanthine, xanthine, uric acid, or uridine in the inosine loading and control studies (Table 3).

*Effect of Inosine on the Concentration of Uridine in Mahlavu Cell Medium*

The concentration of uridine added to medium decreased to 29.5 ± 2.1 μmol/L (n = 3) at 30 minutes, and 14.3 ± 1.1 μmol/L (n = 3) at 1 hour after replacement with fresh medium containing 50 μmol/L uridine, while the concentration of uridine in medium was 37.6 ± 0.5 μmol/L (n = 3) at 30 minutes, and 24.7 ± 0.9 μmol/L (n = 3) at 1 hour after the replacement of fresh culture medium containing both 50 μmol/L uridine and 50 μmol/L inosine (Fig 1). The concentration of uridine added to medium also decreased to 12.6 ± 0.5 μmol/L (n = 3) at 30 minutes, and 1.7 ± 0.3 μmol/L (n = 3) at 1 hour after replacement with the fresh medium containing 25 μmol/L uridine (Fig 1), while the concentration of uridine in medium was 16.2 ± 0.9 μmol/L (n = 3) at 30 minutes, and 7.7 ± 0.5 μmol/L (n = 3) at 1 hour after replacement with fresh culture medium containing 50 μmol/L uridine and 50 μmol/L inosine (Fig 1).

*Effect of Inosine on Uridine Uptake of Mahlavu Cells*

In Mahlavu cells, at a uridine concentration of 50 μmol/L, uridine uptake by Na-independent pathway was linearly increased to 60 seconds (0.69 ± 0.08 pmol/mg protein at 30 seconds and 1.15 ± 0.08 pmol/mg protein at 60 seconds), while uridine uptake by Na-dependent + Na-independent pathways was also linearly increased (0.72 ± 0.12 pmol/mg protein at 30 seconds and 1.17 ± 0.04 pmol/mg protein at 60 seconds). The Na-independent pathway accounted for most of the uridine

**Table 3. Effect of Inosine on the Fractional Clearance of Purine Bases and Uridine, and the Clearance of Creatinine (n = 5)**

| | First Period | Second Period | Third Period | Fourth Period |
|---|---|---|---|---|
| Inosine ingestion | | | | |
| Fhx | 68.2 ± 12.4 | 65.6 ± 10.3 | 78.2 ± 11.2 | 75.9 ± 13.8 |
| Fx | 59.8 ± 15.8 | 56.4 ± 13.5 | 59.0 ± 21.3 | 66.9 ± 20.0 |
| Fua | 7.9 ± 0.5 | 8.6 ± 0.8 | 8.9 ± 1.4 | 9.1 ± 1.4 |
| Fur | 0.33 ± 0.08 | 0.32 ± 0.07 | 0.31 ± 0.08 | 0.31 ± 0.09 |
| CCr | 101 ± 5 | 103 ± 5 | 102 ± 2 | 100 ± 4 |
| Control | | | | |
| Fhx | 73.3 ± 10.0 | 71.4 ± 5.9 | 71.2 ± 5.6 | 67.8 ± 5.3 |
| Fx | 59.5 ± 14.6 | 60.1 ± 15.8 | 60.3 ± 15.5 | 60.8 ± 16.2 |
| Fua | 7.9 ± 0.6 | 7.7 ± 0.9 | 7.9 ± 0.8 | 8.1 ± 0.9 |
| Fur | 0.31 ± 0.07 | 0.32 ± 0.07 | 0.31 ± 0.07 | 0.31 ± 0.06 |
| CCr | 101 ± 3 | 101 ± 5 | 102 ± 3 | 100 ± 4 |

NOTE. Values are expressed as mean ± SD. First, second, third, and fourth periods are the same as described in Table 1.
Abbreviations: Fhx, Fx, Fua, Fur, and CCr denote the percentage ratios of hypoxanthine clearance/creatinine clearance (fractional hypoxanthine clearance), xanthine clearance/creatinine clearance (fractional xanthine clearance), uric acid clearance/creatinine clearance (fractional uric acid clearance), uridine clearance/creatinine clearance (fractional uridine clearance), and creatinine clearance.

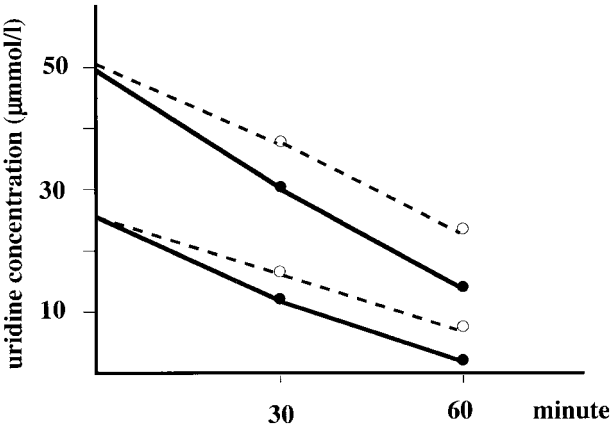


**Fig 1. The effect of inosine on the concentration of uridine added to media. Uridine (25 or 50 μmol/L) was added to fresh media with (○) or without (●) the addition of inosine (50 μmol/L).**

uptake. The apparent Km and Vmax values for Na-independent nucleoside transport obtained during 30 seconds of incubation were 67.0 ± 4.3 μmol/L and 7.0 ± 0.3 pmol/mg protein/s, respectively, and the Ki value of inosine for the Na-independent pathway was 45.1 ± 12.1 μmol/L (Fig 2).

## DISCUSSION

In the present study, inosine increased the plasma concentration and urinary excretion of uridine, uric acid, hypoxanthine, and xanthine; however, it did not affect their clearance (Tables 1 through 3). Previous studies[3,4] have demonstrated that the abrupt degradation of adenine nucleotides by fructose or xylitol increases the plasma concentration and urinary excretion of purine bases, indicating that the abrupt loss of ATP increases purine and pyrimidine degradation. Similar results (an increase in plasma levels of uridine and uric acid as well as the urinary excretion of uric acid) were obtained in the present subjects following an oral administration of inosine; however, the mechanism seems to be different from that involved with ATP consumption-induced purine and pyrimidine degradation. Inosine is a purine nucleoside that is metabolized to hypoxanthine by purine nucleoside phosphorylase, and further to xanthine and uric acid by xanthine dehydrogenase. Since hypoxanthine is salvaged and converted to inosine monophosphate using phosphoribosyl pyrophosphate, the synthesis of purine nucleotides may be accelerated. However, an increase in the synthesis of purine nucleotides does not cause pyrimidine degradation leading to an increased plasma level of uridine. Glucagon, dibutyryl cyclic AMP, and insulin have each been shown to decrease uridine uptake into cells in vitro.[1] In addition, glucagon and dibutyryl cyclic AMP were found to decrease the plasma concentration of uridine in vivo.[8,9] These results suggest that the nucleoside transport pathway plays an important role in the plasma concentration of uridine. In a recent in vitro study, inosine inhibited uridine uptake into A549 cells (a lung cancer cell line).[11] In addition, in the present in vitro study , Mahlavu cells from hepatoma cell line, were able to uptake uridine via the Na-independent nucleoside transport (apparent Km value, 67.0 ± 4.3 μmol/L) and uridine uptake was competitively inhibited by inosine (apparent Ki value, 45.1 ± 12.1 μmol/L). Though the apparent Km value for Na-dependent uridine transport could not be obtained in the present study, in a previous report,[14] inosine inhibited uridine transport via an Na-dependent nucleoside pathway. Therefore, the increase in plasma uridine levels seen in the present data suggests that exogenous inosine inhibits uridine uptake into intestinal epithelial cells via the nucleoside transport. Moreover, it is also suggested that a considerable amount of uridine is actively transported from plasma into cells in the intestine and liver in humans, since we found that the plasma concentration of uridine rapidly increased by approximately 1 μmol/L at 2.5 hours after inosine intake.

An increase in the plasma concentration of uridine may not only be a marker of pyrimidine degradation, such as in fructose infusion, xylitol infusion, ethanol ingestion, or muscle exercise,[3-5] but also be a marker of uridine transport inhibition, such as in inosine administration.

Uridine may have other physiological actions, besides nucleic biosynthesis, as it is found in considerably higher quantities than other purine and pyrimidine nucleosides in human plasma. In a previous study,[15] it was shown that uridine had a vasoconstrictive effect in rats, and that effect was reduced by adenosine. Another study[16] demonstrated that plasma uridine levels in deoxycorticosterone (DOCA)-salt hypertensive rats were reduced as compared with control rats, indicating that the metabolic clearance of uridine in these rats was raised and that uridine may be associated with vasoconstriction.[15] However, in humans, the physiological action of plasma uridine remains undetermined; thus, further examination is required to clarify its physiological effects.

In the present study with purine bases, as expected, inosine ingestion rapidly increased the plasma concentration and urinary excretion of uric acid, while those of oxypurines increased only slightly. Our results indicate that the exogenous inosine is taken up rapidly in the intestinal epithelial and liver cells, and

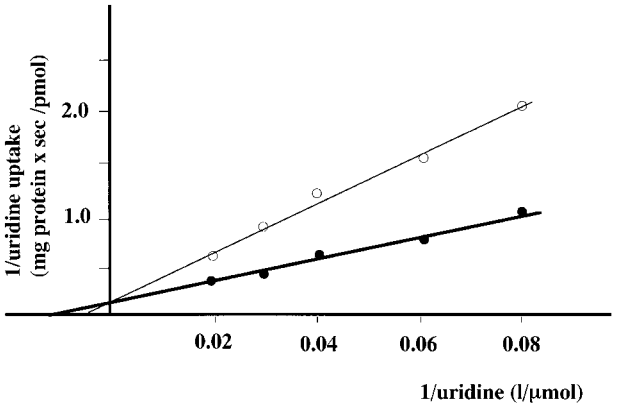


**Fig 2. Double reciprocal plots of uridine uptake. ●, without the addition of 50 μmol/L inosine; ○, with the addition of 50 μmol/L inosine.**

mostly metabolized to hypoxanthine by purine nucleoside phosphorylase and next to uric acid via xanthine by xanthine dehydrogenase. It is also suggested that the small intestine and liver possess purine nucleoside phosphorylase and xanthine dehydrogenase in large enough quantities to metabolize inosine to uric acid via hypoxanthine and xanthine in humans.

## REFERENCES

1. Gomez-Angelats M, del Santo B, Mercader J, et al; Hormonal regulation of concentrative nucleoside transport in liver parenchymal cells. Biochem J 313:915-920, 1996

2. Ruiz-Montasell B, Martinez-Mas JV, Enrich C, et al: Early induction of Na-dependent uridine uptake in the regenerating rat liver. FEBS Lett 316:85-88, 1993

3. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effects of fructose and xylitol on the urinary excretion of adenosine, uridine and purine bases. Metabolism 48:520-524, 1999

4. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effect of ethanol and fructose on plasma uridine and purine bases. Metabolism 46:544-547, 1997

5. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effect of muscular exercise on the concentration of uridine and purine bases in plasma-ATP consumption-induced pyrimidine degradation. Metabolism 46: 1339-1342, 1997

6. Yamamoto T, Moriwaki Y, Takahashi S, et al: Xylitol-induced increase in the plasma concentration and urinary excretion of uridine and purine bases. Metabolism 47:739-743, 1998

7. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effect of glucose on plasma concentrations and urinary excretion of uridine and purine bases. Metabolism 148:338-341,1999

8. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effect of glucagon on the plasma concentration of uridine. Metabolism 47:695-698, 1998

9. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effect of bucladesine sodium on the plasma concentrations and urinary excretion of purine bases and uridine. Metabolism 47:1005-1008, 1998

10. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effect of amino acids on the plasma concentrations and urinary excretion of uric acid and uridine. Metabolism 48:1023-1027, 1999

11. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effect of TEI-6720, a xanthine oxidase inhibitor on nucleoside transport in the lung cancer cell line A549. Pharmacology 60:34-40, 2000

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

13. Yamamoto T, Moriwaki Y, Takahashi S, et al: Effect of branched-chain amino acids on the plasma concentration of uridine is not via the action of glucagon or insulin. Metabolism 49:97-100, 2000

14. Mercader J, Gomez-Angelats M, del Santo B, et al: Nucleoside uptake in rat liver parenchymal cells. Biochem J 317:835-842, 1996

15. Macdonald G, Assef R, Guiffre A, et al: Vasoconstrictor effects of uridine and its nucleotides and their inhibition by adenosine. Clin Exp Pharmacol Physiol 11:381-384, 1984

16. Hasnain Q, Macdonald G: Metabolic studies of uridine in rats with DOCA-salt hypertension and on high sodium diet. Clin Exp Pharmacol Physiol 20:384-387, 1993