Effect of Amino Acids on the Plasma Concentration and Urinary Excretion of Uric Acid and Uridine

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To determine the effect of amino acids on the plasma level and urinary excretion of uric acid and uridine, 200 mL 12% amino acid solution, and 2 weeks later, 100 mL physiological saline solution containing glucagon (1.2 μg/kg weight), was infused into five healthy men. Both increased the urinary excretion of uric acid and the concentration of glucagon, insulin, and glucose in plasma and pyruvic acid in blood, whereas they decreased the concentration of uridine and inorganic phosphate in plasma. However, neither the amino acid infusion nor glucagon infusion affected the concentration of purine bases (hypoxanthine, xanthine, and uric acid), cyclic adenosine monophosphate (cAMP) in plasma, or lactic acid in blood or the urinary excretion of oxypurines (hypoxanthine and xanthine), uridine, or sodium. These results suggest that glucagon may have an important role in the amino acid–induced increase in urinary excretion of uric acid and decrease in plasma uridine.

PREVIOUS STUDIES have demonstrated that amino acids and protein increase the urinary excretion of uric acid,[1-3] although the mechanism remains undetermined. Recently, we demonstrated that a pharmacological dose of glucagon increases the urinary excretion of uric acid and oxypurinol,[4] suggesting that an amino acid– or protein-induced increase in the plasma concentration of glucagon in the portal vein may cause increased urinary excretion of uric acid. In addition, we demonstrated that glucagon[5] and dibutyryl cyclic adenosine monophosphate (cAMP)[6] decrease the plasma concentration of uridine together with an increase in the urinary excretion of uric acid. The mechanism(s) for the glucagon or cAMP-induced decrease in the plasma concentration of uridine remains undetermined. However, a recent study[7] showed that glucagon and dibutyryl cAMP enhance uridine uptake into cells via a Na-dependent nucleoside transport pathway in vitro, suggesting that glucagon stimulates the production of cAMP and enhances the uptake of uridine into cells via the effect of cAMP. Further, it has been suggested that the physiological role of the Na-dependent nucleoside transport pathway is to preserve extracellular nucleoside for endogenous synthesis of nucleic acids,[7,8] since this nucleoside transport is enhanced in response to a mitogenic stimulus such as partial hepatectomy.[8] Another study[7] suggests that enhancement of the nucleoside transport by glucagon may have a clinically beneficial role in nucleic biosynthesis in a physiological condition that leads to hypertrophia and hyperplasia of the liver. However, the effect of glucagon on the plasma concentration of uridine was found to be pharmacological in a recent study.[5]

Since amino acids have been shown to stimulate glucagon secretion from cells in pancreatic islets and to increase the plasma concentration of glucagon in the portal vein, they may decrease the plasma concentration of uridine and increase the urinary excretion of uric acid via the action of glucagon. Therefore, in the present study, we examined whether an amino acid infusion decreases the plasma concentration of uridine and increases the urinary excretion of uric acid, using an amino acid solution with the same protein composition as human milk. Further, to elucidate whether glucagon plays an important role in these actions, a glucagon infusion was administered at the physiological plasma level in the portal vein.

SUBJECTS AND METHODS

Chemicals

Uridine, hypoxanthine, xanthine, and uric acid were purchased from Sigma Chemical (St Louis, MO). A 12% amino acid solution (Table 1) was purchased from Japan Pharmaceuticals (Tokyo, Japan). Glucagon was obtained from Novo Nordisk (Copenhagen, Denmark). Other chemicals were obtained from Wako Pure Chemicals (Osaka, Japan).

Subjects and Protocol

After obtaining informed consent, we performed the first study on five healthy subjects aged 32 to 50 years, using a 12% amino acid solution to increase urinary uric acid excretion[1] in similarity to a high-protein diet. After an overnight fast except for water, the 1-hour urine sample was collected and 200 mL 12% amino acid solution was infused for 1 hour. After the amino acids were infused, another 1-hour urine sample was collected immediately. In addition, blood was drawn using heparinized syringes at the midpoint of each urinary collection and the end of the amino acid infusion. Two weeks later, a second study was performed. The protocol was the same as described for the first study, except that a physiological saline solution (100 mL) containing 1.2 μg glucagon/kg body weight was infused instead of the amino acid solution. The amino acid solution increased the plasma glucagon level and urinary uric acid excretion in a preliminary study.

Blood and Urine Analyses

Plasma concentrations of uridine, hypoxanthine, and xanthine and urinary concentrations of hypoxanthine and xanthine were determined by high-performance liquid chromatography (HPLC) as described previously.[1] The urinary concentration of uridine was determined by HPLC with column-switching as follows. The chromatograph consisted of two CCPM pumps (Tosoh, Tokyo, Japan), an SC-8020 system controller (Tosoh), two spectrophotometric detectors (UV-8010 and UV-8020; Tosoh), and a VC-8020 column-switching valve (Tosoh). The chromatographic columns used were a Wakosil 5C18-200 (4.6 × 250 mm; Wako Pure Chemicals, Osaka, Japan) as the first column and a Tosoh TSK Gel ODS-120A (4.6 × 250 mm) as the second column. In

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Table 1. Composition of the Amino Acid Solution (200 mL)

Component	Amount (mmol)
Aspartic acid	9.0
Threonine	10.0
Serine	4.6
Glutamic acid	2.5
Proline	4.2
Glycine	48.6
Alanine	10.8
Valine	14.8
Cysteine	0.2
Methionine	7.3
Isoleucine	12.9
Leucine	17.9
Phenylalanine	15.5
Histidine hydrochloride	6.3
Tryptophan	2.2
Arginine hydrochloride	11.4
Tyrosine	0.7
Na^+	13
Cl^-	30

both columns, the mobile phase was 20 mmol/L KH_2PO_4 (pH 2.2), the flow rate 1 mL/min, and the detection wavelength 254 nm. Twenty microliters of urine without dilution was applied to the first column. At the fraction time at which uridine was eluted via the first column, the two 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 as described previously.[1] The concentrations of lactic acid and pyruvic acid in blood and glucagon and cAMP in plasma were also determined as described previously.[4] The percentage ratios for hypoxanthine clearance to creatinine clearance (fractional hypoxanthine clearance), xanthine clearance to creatinine clearance (fractional xanthine clearance), uric acid clearance to creatinine clearance (fractional uric acid clearance), and uridine clearance to creatinine clearance (fractional uridine clearance) were calculated, together with creatinine clearance, using the values for plasma samples drawn 30 minutes before and after the beginning of the amino acid infusion.

Statistical Analysis

Values are reported as the mean ± SD. Significant differences between mean values were analyzed by a two-tailed paired *t* test.

RESULTS

Effects of Amino Acid Infusion

Plasma concentration of purine bases and uridine. Amino acid infusion did not affect plasma concentrations of hypoxanthine, xanthine, or uric acid during the study, whereas it decreased the plasma concentration of uridine by 25.1% at 30 minutes and 58.5% at 1 hour after beginning the infusion as compared with the value 30 minutes before infusion (Table 2).

Urinary excretion of purine bases, uridine, sodium, and inorganic phosphate. Amino acid infusion increased the urinary excretion of uric acid by 61% compared with the preinfusion value. However, it did not affect urinary excretion of hypoxanthine, xanthine, uridine, sodium (8.21 ± 4.13 *v* 5.40 ± 2.69 mmol/h), or inorganic phosphate (7.90 ± 2.70 *v* 9.87 ± 2.73 mmol/h) (Table 3).

Table 2. Effect of Amino Acids on the Concentration of Hypoxanthine, Xanthine, Uric Acid, and Uridine in Plasma

	Period		
Variable	1	2	3
Hypoxanthine	1.46 ± 0.78	1.50 ± 0.80	1.32 ± 0.74
Xanthine	0.54 ± 0.08	0.44 ± 0.07	0.50 ± 0.08
Uric acid	342 ± 32	342 ± 26	338 ± 35
Uridine	4.38 ± 0.86	3.28 ± 0.96*	1.82 ± 0.14*

NOTE. Values are the mean ± SD (μmol/L). Periods: 1, 30 minutes before infusion; 2, 30 minutes after beginning the infusion; 3, 1 hour after beginning the infusion.

*$P < .01$ *v* period 1.

Clearance of creatinine and fractional clearance of hypoxanthine, xanthine, uric acid, and uridine. Amino acid infusion increased the fractional clearance of uric acid by 60%, but did not affect the clearance of creatinine or fractional clearance of hypoxanthine, xanthine, or uridine (Table 4).

Plasma concentrations of glucagon, insulin, and cAMP. Amino acid infusion increased plasma concentrations of glucagon and insulin 2.5- and 8.1-fold at 30 minutes and 2.8- and 9.3-fold at 1 hour, respectively, after beginning the infusion as compared with 30 minutes before the infusion, but it did not affect the plasma concentration of cAMP (Table 5).

Concentrations of lactic acid and pyruvic acid in blood and glucose, inorganic phosphate, and sodium in plasma. Amino acid infusion did not affect the blood concentration of lactic acid, but increased blood pyruvic acid by 23% and 25% at 30 minutes and 1 hour, respectively, after beginning the infusion, and it also increased blood glucose by 11% at 30 minutes after beginning the infusion as compared with the respective preinfusion values. The amino acid infusion did not affect the plasma concentration of sodium, but decreased plasma inorganic phosphate by 12% and 27% at 30 minutes and 1 hour, respectively, after beginning the infusion, as compared with 30 minutes before the infusion (Table 6).

Effects of Glucagon Infusion

Plasma concentration of purine bases and uridine. Glucagon infusion did not affect plasma concentrations of hypoxanthine, xanthine, or uric acid during the study, whereas it decreased the plasma concentration of uridine by 12% and 33% at 30 minutes and 1 hour, respectively, after beginning the infusion as compared with the value at 30 minutes before infusion (Table 7). These results were similar to those in the amino acid infusion study.

Table 3. Effect of Amino Acids on the Urinary Excretion of Hypoxanthine, Xanthine, Uric Acid, and Uridine

	Period	
Variable	A	B
Hypoxanthine	4.42 ± 1.18	3.78 ± 1.39
Xanthine	2.58 ± 0.79	2.81 ± 0.81
Uric acid	181 ± 49	292 ± 41*
Uridine	0.24 ± 0.14	0.19 ± 0.12

NOTE. Values are the mean ± SD (μmol/h). Periods: A, 1 hour before infusion; B, 1 hour after beginning the infusion.

*$P < .01$ *v* period 1.

Table 4. Effect of Amino Acids on the Clearance of Creatinine and Fractional Clearance of Hypoxanthine, Xanthine, Uric Acid, and Uridine

Variable	Period A	Period B
Creatinine clearance (mL/min)	99.5 ± 7.1	102.0 ± 4.7
Fractional clearance (mL/min/mL/min × 100)		
Hypoxanthine	65.2 ± 38.5	59.2 ± 53.0
Xanthine	79.4 ± 15.4	63.0 ± 11.1
Uric acid	8.8 ± 1.5	14.1 ± 2.7*
Uridine	0.88 ± 0.46	0.97 ± 0 66

NOTE. Values are the mean ± SD. Fractional clearance of hypoxanthine, xanthine, uric acid, and uridine denotes the percentage ratios for hypoxanthine clearance/creatinine clearance, xanthine clearance/creatinine clearance, uric acid clearance/creatinine clearance, and uridine clearance/creatinine clearance, respectively. Periods: A, 1 hour before infusion; B, 1 hour after beginning the infusion.

*$P < .01$ *v* basal value.

Urinary excretion of purine bases, uridine, sodium, and inorganic phosphate. Glucagon infusion increased the urinary excretion of uric acid by 22% compared with the preinfusion value, whereas it did not affect urinary excretion of hypoxanthine, xanthine, uridine, sodium (6.8 ± 3.8 *v* 7.4 ± 4.0 mmol/h). or inorganic phosphate (7.61 ± 2.12 *v* 8.65 ± 3.00 mmol/h) (Table 8). These results also were similar to those in the amino acid infusion study.

Clearance of creatinine and fractional clearance of hypoxanthine, xanthine, uric acid, and uridine. Glucagon infusion increased the fractional clearance of uric acid by 34%, but did not affect the clearance of creatinine or fractional clearance of hypoxanthine, xanthine, or uridine (Table 9).

Plasma concentrations of glucagon, insulin, and cAMP. Glucagon infusion increased plasma concentrations of glucagon and insulin 8.1- and 4.1-fold at 30 minutes and 8.8- and 5.0-fold at 1 hour. respectively, after beginning the infusion as compared with the respective values at 30 minutes before infusion, whereas it did not affect the plasma concentration of cAMP (Table 10).

Concentrations of lactic acid and pyruvic acid in blood, and glucose, inorganic phosphate, and sodium in plasma. Glucagon infusion did not affect the blood concentration of lactic acid, but it increased blood pyruvic acid by 29% at 1 hour after beginning the infusion as compared with 30 minutes before infusion. It increased blood glucose by 50% at 30 minutes and 49% at 1 hour after beginning the infusion, and decreased plasma inorganic phosphate by 18% at 30 minutes and 27% at 1 hour after beginning the infusion, as compared with the respective values at 30 minutes before the infusion. However, it did not affect the plasma concentration of sodium (Table 11).

Table 5. Effect of Amino Acids on the Plasma Concentration of Glucagon, Insulin, and cAMP

Variable	Period 1	Period 2	Period 3
Glucagon (pg/mL)	91 ± 32	230 ± 21*	256 ± 30*
Insulin (μU/mL)	4.8 ± 2.5	39.0 ± 17.0*	44.4 ± 15 5*
cAMP (nmol/L)	13.1 ± 2.3	15.6 ± 4 9	15.4 ± 3.2

NOTE. Values are the mean ± SD. Periods: 1, 30 minutes before infusion; 2, 30 minutes after beginning the infusion; 3, 1 hour after beginning the infusion.

*$P < .01$ *v* period 1.

Table 6. Effect of Amino Acids on the Concentration of Lactic Acid and Pyruvic Acid in Blood and Glucose and Inorganic Phosphate in Plasma

Variable	Period 1	Period 2	Period 3
Lactic acid	1.04 ± 0.34	1.16 ± 0.32	1.12 ± 0.21
Pyruvic acid	0.061 ± 0.027	0.075 ± 0.022†	0.076 ± 0.022†
Glucose	5.50 ± 0.192	6.09 ± 0 155*	5.83 ± 0.18
Inorganic phosphate	0.99 ± 0.15	0.87 ± 0.13†	0.73 ± 0.13†
Na^+	142 ± 2	141 ± 1	141 ± 1

NOTE. Values are the mean ± SD (mmol/L). Periods. 1, 30 minutes before infusion; 2, 30 minutes after beginning the infusion, 3, 1 hour after beginning the infusion.

*$P < .05$, †$P < .01$: *v* period 1.

DISCUSSION

In the present study, an amino acid infusion increased the urinary excretion of uric acid without affecting the plasma concentration of uric acid or the plasma concentration and urinary excretion of oxypurines (hypoxanthine and xanthine) (Tables 2 to 4). These results indicate that amino acids increased the urinary excretion of uric acid via renal transport of uric acid, but they did not affect purine degradation. In a recent study,[5] similar results were obtained with a pharmacological dose of glucagon, suggesting that an amino acid– or protein-induced increase in the plasma concentration of glucagon in the portal vein may cause increased urinary excretion of uric acid via the release of a supposedly liver-derived factor (vasodilator), since the glucagon receptor was not detected at the proximal tubules in rat kidneys.[9,10] Further, in another recent study by our group,[6] bucladesine sodium (dibutyryl cAMP) increased the urinary excretion of uric acid, suggesting that cAMP increases urinary excretion of uric acid. However, in the present study, although an amino acid infusion increased the plasma concentration of glucagon together with the urinary excretion of uric acid, it did not increase the plasma concentration of cAMP (Table 4). Although amino acids are known to increase the renal clearance of uric acid directly by virtue of being weak organic acids, glucagon may have an important role in an amino acid–induced increase in the renal clearance of uric acid. Therefore, to determine whether an increased glucagon level in the portal

Table 7. Effect of Glucagon on the Concentration of Hypoxanthine, Xanthine, Uric Acid, and Uridine in Plasma

Variable	Period 1	Period 2	Period 3
Hypoxanthine	1.06 ± 0.60	0.98 ± 0.52	1 02 ± 0 38
Xanthine	0.68 ± 0.22	0.60 ± 0 11	0.70 ± 0.26
Uric acid	330 ± 45	331 ± 46	311 ± 43
Uridine	4.24 ± 0.86	3.72 ± 0.70*	2.82 ± 0.83*

NOTE. Values are the mean ± SD (μmol/L). Periods: 1, 30 minutes before infusion; 2, 30 minutes after beginning the infusion; 3, 1 hour after beginning the infusion

*$P < .01$ *v* period 1.

Table 8. Effect of Glucagon on the Urinary Excretion of Hypoxanthine, Xanthine, Uric Acid, and Uridine

Variable	Period A	Period B
Hypoxanthine	5.19 ± 2.07	5.60 ± 1.99
Xanthine	3.16 ± 1.26	3.60 ± 1.27
Uric acid	145 ± 34	206 ± 34*
Uridine	0.16 ± 0.10	0.15 ± 0.08

NOTE. Values are the mean ± SD (μmol/h). Periods: A, 1 hour before infusion; B, 1 hour after beginning the infusion.
*$P < .01$ *v* period 1.

Table 10. Effect of Glucagon on the Plasma Concentration of Glucagon, Insulin, and cAMP

Variable	Period 1	Period 2	Period 3
Glucagon (pg/mL)	100 ± 39.5	812 ± 242*	876 ± 79.6*
Insulin (μU/mL)	4.9 ± 1.8	20.0 ± 6.0*	24.6 ± 4.2*
cAMP (μmol/L)	11.7 ± 2.0	17.0 ± 4.3	15.4 ± 2.2

NOTE. Values are the mean ± SD. Periods: 1, 30 minutes before infusion; 2, 30 minutes after beginning the infusion; 3, 1 hour after beginning the infusion.
*$P < .01$ *v* period 1.

vein plays a role in the amino acid–induced increase in urinary excretion of uric acid, we infused small amounts of glucagon, which were sufficient to obtain the plasma concentration of glucagon in the portal vein inferred during the amino acid infusion, since the plasma concentration of glucagon in the portal vein has been shown to be two to 2.5 times higher than the concentration in the artery and inferior vena cava upon meat ingestion or exercise.[11,12] As expected, administration of small amounts of glucagon increased the urinary excretion of uric acid (Table 8), suggesting that increased glucagon in the portal vein plays an important role in the increase in urinary excretion of uric acid induced by amino acid infusion (Tables 3 and 4). Our previous studies[4,5] demonstrated that a pharmacological dose of glucagon increased the plasma concentration of natriuresis-inducing cAMP and the urinary excretion of uric acid and sodium. However, in the present study, the plasma concentration of cAMP and urinary excretion of sodium were not increased by amino acids or small amounts of glucagon, suggesting that cAMP does not cause the increased urinary excretion of uric acid with amino acid or glucagon infusion.

In the present study, it was also demonstrated that amino acid infusion decreases the plasma concentration of uridine (Table 2). Since enhanced purine degradation[13-17] increases the degradation of uracil nucleotides, leading to an increased plasma concentration of uridine, a decrease in the plasma concentration and urinary excretion of uridine may be related to purine metabolism. However, as already described, amino acids did not affect purine metabolism in the present study (Tables 2 and 3). Therefore, other factors must be considered as the cause of the amino acid–induced decrease in the plasma concentration of uridine.

One potential factor is an amino acid–induced increase in urinary excretion of uridine. However, since urinary excretion of uridine did not increase during amino acid infusion (Table 3), this possibility is negated. Another possible factor is a decrease in glycogenesis. Recently, we demonstrated that the plasma concentration of uridine is transiently increased by oral administration of 75 g glucose, which increases the plasma concentration of insulin and accelerates glycogenesis.[18] In glycogenesis, glucose is phosphorylated to glucose-6-phosphate using adenosine triphosphate and converted to glucose-1-phosphate. In the next step, uridine diphosphoglucose (UDP-glucose) is formed from glucose-1-phosphate and uridine triphosphate, and in the final step, glycogen is synthesized from UDP-glucose together with the release of uridine diphosphate (UDP). Therefore, a glucose-induced increase in the plasma concentration of uridine suggests that UDP released from UDP-glucose increases abruptly along with an abrupt decrease in UDP-glucose[19] via glycogenesis after oral administration of glucose, leading to UDP degradation (UDP → uridine monophosphate → uridine). However, since oral administration of casein leads to an increase in the portal plasma concentration of glucagon and a decrease in the hepatic concentration of glycogen but does not affect UDP-glucose in rats,[20] it is suggested that amino acids, as well as casein, may not affect the hepatic concentration of UDP-glucose. Further, insulin must be considered as another factor, since it stimulates the formation of uracil nucleotides from uridine in skeletal muscle, the major body compartment,[21] and

Table 9. Effect of Glucagon on the Clearance of Creatinine and Fractional Clearance of Hypoxanthine, Xanthine, Uric Acid, and Uridine

Variable	Period A	Period B
Creatinine clearance (mL/min)	95.8 ± 7 3	102.8 ± 10.1
Fractional clearance (mL/min/mL/min × 100)		
Hypoxanthine	90.3 ± 18	98.8 ± 15.0
Xanthine	78.1 ± 14.1	94.8 ± 20.4
Uric acid	7.6 ± 1.2	10.2 ± 1.9*
Uridine	0.65 ± 0.41	0.68 ± 0.43

NOTE. Values are the mean ± SD. Fractional clearance of hypoxanthine, xanthine, uric acid, and uridine denotes the percentage ratios for hypoxanthine clearance/creatinine clearance, xanthine clearance/creatinine clearance, uric acid clearance/creatinine clearance, and uridine clearance/creatinine clearance, respectively. Periods: A, 1 hour before infusion; B, 1 hour after beginning the infusion.
*$P < .01$ *v* basal value.

Table 11. Effect of Glucagon on the Concentration of Lactic Acid and Pyruvic Acid in Blood and Glucose and Inorganic Phosphate in Plasma

Variable	Period 1	Period 2	Period 3
Lactic acid	0.81 ± 0.30	0.85 ± 0.22	0.98 ± 0 31
Pyruvic acid	0.051 ± 0.023	0.053 ± 0.028	0.066 ± 0.028*
Glucose	5.53 ± 0.31	8.31 ± 0.83*	8.23 ± 1.09*
Inorganic phosphate	1.06 ± 0.12	0.87 ± 0.20*	0.77 ± 0.15*
Na^+	142 ± 1	142 ± 2	142 ± 1

NOTE. Values are the mean ± SD (mmol/L). Periods: 1, 30 minutes before infusion; 2, 30 minutes after beginning the infusion; 3, 1 hour after beginning the infusion.
*$P < .01$ *v* period 1.

accelerates uridine uptake via the Na-dependent nucleoside transport pathway in vitro.[7] Since both the amino acid infusion and glucagon infusion increased the plasma concentration of insulin in the present study (Tables 5 and 10), insulin may play a role in an amino acid–induced decrease in the plasma concentration of uridine without an enhancement of glycogenesis. However, the most probable factor is glucagon that accelerates the uptake of uridine into cells in vitro. In fact, the present study demonstrated that both the amino acid infusion and glucagon infusion increased the plasma concentration of glucagon and decreased plasma uridine (Tables 2, 5, 7, and 10), suggesting that glucagon is a factor in the amino acid–induced decrease in the plasma concentration of uridine, and also that the physiological role of the Na-dependent nucleoside transport pathway is to preserve extracellular nucleoside for the endogenous synthesis of nucleic acids.[7,8] Further, the present study also demonstrated that decreases in the plasma concentration of uridine and inorganic phosphate along with the increase in the blood concentration of pyruvic acid were similar for the amino acid infusion (Tables 2 and 6) and glucagon infusion (Tables 7 and 11).

These results suggest the possibility that glucagon released from the islets by amino acid infusion decreased the plasma concentration of uridine. In addition, it is suggested that an amino acid–induced increase in the plasma concentration of glucagon in the portal vein may increase the hepatic concentration of cAMP sufficiently to accelerate the uptake of uridine but not to increase the plasma concentration of cAMP in peripheral veins, since a previous in vitro study suggests that the effect of glucagon on uridine may be dependent on cAMP in hepatic cells.[7] However, to rule out the possibility of other unknown factors, further studies are required, including administration of amino acids together with somatostatin, since somatostatin inhibits the secretion of insulin and glucagon from islets.

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