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

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Abstract. To determine the effect of octreotide acetate on urinary excretion of uric acid and plasma concentration of uridine, we subcutaneously administered octreotide acetate (1 μg/kg of body weight) to 5 healthy subjects. Ninety minutes after administration, octreotide acetate increased the plasma concentration of uridine by 15% and decreased the plasma concentration of glucagon by 24% and that of insulin to below the detection limits. In addition, octreotide acetate decreased the urinary excretion of uric acid, sodium, and chloride by 60%, 40%, and 38%, respectively, at 1 hour after administration. However, octreotide acetate did not affect the concentrations of hypoxanthine, xanthine, uric acid, cyclic AMP in plasma, lactic acid and pyruvic acid in blood, urinary excretion of hypoxanthine and xanthine, or creatinine clearance. From these results, we speculated that octreotide acetate decreases the urinary excretion of uric acid by decreasing the concentration of glucagon and/or urinary excretion of sodium, and increases the plasma concentration of uridine via decreased concentrations of glucagon and insulin.

Key words: Octreotide acetate, Uric acid, Uridine, Glucagon, Insulin

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OCTREOTIDE acetate, a somatostatin analog, inhibits the secretion of insulin and glucagon. It does not significantly affect creatinine clearance which reflects the glomerular filtration rate (GFR), but it does decrease the urinary excretion of sodium, chloride, and calcium (as does somatostatin), suggesting a direct tubular effect of octreotide acetate [1]. Uric acid, an end-product of purine degradation, is oxidized by xanthine dehydrogenase and approximately 70% of it is excreted through the kidneys. Urinary excretion of uric acid is decreased by many factors including lactic acid, pyrazinamide (an anti-tuberculous agent), and insulin [2–4], and is increased by several factors such as glucagon, pyruvic acid, sodium infusion, and uricosuric agents benzbromarone and probenecid [3, 5–7]. Glucagon increases the urinary excretion of uric acid and sodium [6, 8–10], while insulin decreases them, and the reabsorption of sodium may be coupled with that of uric acid in the kidneys [11–13]. Therefore, the effect of octreotide acetate on the secretion of glucagon and insulin and the urinary excretion of sodium suggests that it may affect the urinary excretion of uric acid.

Uridine, a pyrimidine nucleoside, is an essential substance for RNA synthesis. Plasma uridine is transported into cells via the nucleoside transport pathways for the endogenous synthesis of nucleic acids. In addition to nucleic biosynthesis, uridine may have other physiological actions, as it is found in considerably higher quantities than other purine and pyrimidine nucleosides in human plasma. In a previous report [14], it was found that uridine had a vasoconstrictive effect in rats, which was reversed by adenosine. In another study [15], it was demonstrated that plasma uridine levels in deoxycorticoster-

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one (DOCA)-salt hypertensive rats were reduced when compared with control rats, indicating that the metabolic clearance of uridine in DOCA-salt hypertensive rats was enhanced and that uridine may be associated with vasoconstriction [14]. However, in humans, the physiological action of plasma uridine remains undetermined. The effect of octreotide acetate on the secretion of glucagon and insulin also suggests that it may decrease the plasma concentration of uridine, since insulin and glucagon enhance uridine uptake into cells via the Na-dependent nucleoside transport pathway *in vitro* [16], and because glucagon decreases the plasma concentration of uridine *in vivo* [10].

Octreotide acetate is clinically used to treat patients with acromegaly and giantism because it inhibits the secretion of growth hormone from pituitary adenoma. Thus, we investigated its effect on the urinary excretion of uric acid and plasma concentration of uridine. The urinary excretion of uric acid is known to be increased by pyruvic acid and inhibited by lactic acid [2, 6], while the plasma concentration of uridine is increased by glucose intake [17] and enhanced purine degradation [8, 18, 19, 20] (as indicated by an increase in plasma concentration of hypoxanthine and xanthine), and is decreased by bucladesine sodium (dibutyryl cAMP) infusion [21]. Accordingly, we also studied the effects of octreotide acetate on lactic acid, pyruvic acid, cyclic AMP, glucose, and oxypurines (hypoxanthine and xanthine) in addition to glucagon and insulin.

Subjects and Methods

Chemical reagents

Uridine, hypoxanthine, xanthine, and uric acid were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Octreotide acetate was purchased from Novartis (Basel, Switzerland). All other chemicals were obtained from Wako Pure Chemicals (Osaka, Japan).

Subjects and Protocol

After obtaining informed consent, we conducted the first study on 5 healthy subjects, who ranged in age from 32 to 50 years old. After an overnight fast except for water, 1-hr urine was collected 3 times over 3 hr, and blood was drawn at the midpoint of each urinary collection by heparinized syringes. Octreotide acetate (1 μg/kg body weight) was administered subcutaneously after the first 1-hr urinary collection. Two weeks later, a control study was performed with the same protocol, except for the subcutaneous administration of physiological saline instead of octreotide acetate. The protocol was approved by the Hyogo College of Medicine Committee on the Protection of Human Subjects in Research.

Blood and urine analyses

Plasma concentrations of uridine, hypoxanthine, and xanthine were determined by high-performance liquid chromatography (HPLC) as described previously [18], as were urinary concentrations of hypoxanthine and xanthine [17]. Urinary concentration of uridine was determined by HPLC with column switching [10] as follows. The chromatograph consisted of two CCPM pumps (Tosoh, Tokyo, Japan), an SC-8020 system controller (Tosoh, Tokyo, Japan), two spectrophotometric detectors (UV-8010 and UV-8020) (Tosoh, Tokyo, Japan) and a VC-8020 column switching valve (Tosoh, Tokyo, Japan). The chromatographic columns 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 both columns, the mobile phase was 20 mM KH2PO4 (pH 2.2), the flow rate, 1 ml/min and detection wavelength, 254 nm. Twenty μl urine without dilution was applied to the first column. At the fraction time in which uridine was eluted via the first column, the two columns were connected and the eluate from the second column was monitored. Plasma and urinary concentrations of uric acid were measured by the uricase method using an autoanalyzer (model 736, Hitachi, Tokyo, Japan). The blood concentrations of lactic acid and pyruvic acid were determined by Determiner LA kit and Determiner PA kit (Kyowa Medix, Tokyo, Japan), respectively. Plasma concentrations of insulin and glucagon were determined by radioimmunoassay using Glucagon kit (Daiichi, Tokyo, Japan) and Insulin Riabead II kit (Dainabot, Tokyo, Japan), respectively. Plasma concentrations of cyclic AMP (cAMP) were also measured by radioimmunoassay, using Cyclic AMP

kit Yamasa (Yamasa Soy Co., Chiba, Japan).

Statistical Analysis

Values are shown as mean±SD. The significance of difference among means was analyzed by ANOVA.

Result

Effect of octreotide acetate on plasma concentrations of purine bases and uridine

Plasma concentrations of hypoxanthine, xanthine, and uric acid did not change after subcutaneous administration of octreotide (Table 1). In contrast, plasma concentration of uridine was increased by 15% at 90 min after administration, as compared with the value 30 min before administration (Table 1). These values did not change significantly in the control study (data not shown).

Effect of octreotide acetate on urinary excretion of purine bases and uridine

Urinary excretion of hypoxanthine, xanthine, and uridine did not change after subcutaneous administration of octreotide acetate (Table 2). In contrast, urinary excretion of uric acid was decreased by 32% at 1 hr, and by 43% at 1 to 2 hr, following administration of octreotide acetate, as compared with baseline value (Table 2). These values did not change significantly in the control study (data not shown).

Effect of octreotide acetate on urine volume, creatinine clearance, and urinary excretion of sodium, and chloride

Urine volume and creatinine clearance did not change significantly after administration of octreotide acetate (Table 2). In contrast, urinary excretion of sodium and chloride decreased by 60% and 40%, respectively, at 1 hr, and by 57% and 40%, respectively, at 1 to 2 hr following administration (Table 2). These values did not change significantly in the control study (data not shown).

Effect of octreotide acetate on plasma concentrations of glucagon, insulin, and cyclic AMP

Plasma concentration of glucagon was decreased by 22% at 30 min, and 24% at 90 min after administration of octreotide acetate, as compared with the value before administration (Table 1). Plasma concentration of insulin also decreased from 5.9±2.1 at 30 min before administration of octreotide acetate to

Table 1. Effect of octreotide acetate on the concentrations of purine bases, uridine, glucagon, insulin, and cyclic AMP in plasma, and glucose, lactic acid, and pyruvic acid in blood (N=5).

	−30	30	90
hypoxanthine (μM)	1.22±0.66	2.04±0.61	1.60±0.52
xanthine (μM)	0.50±0.24	0.54±0.26	0.58±0.28
uric acid (μM)	339±24	339±23	339±30
uridine (μM)	4.52±0.32	4.74±0.42	5.20±0.48*
glucagon (ng/ml)	91±28	71+31**	67+24**
insulin (IU)	5.9±2.1	ND**	ND**
cyclic AMP (ng/ml)	14.0±1.41	12.4±1.7	14.2±2.2
glucose (mM)	5.52±0.21	4.56±0.22**	5.72±0.26
lactic acid (mM)	0.98±0.32	0.89±0.34	0.86±0.42
pyruvic acid (mM)	0.049±0.022	0.050±0.015	0.047±0.019

Values are expressed as mean±SD.
−30, 30, and 90: 30 min before, and 30 and 90 min after, respectively, the administration of octreotide acetate.
* and **: $P<0.05$ and $P<0.01$, respectively, as compared with the value at −30.
ND: not detected.

Table 2. Effect of octreotide acetate on the urinary excretion of purine bases, uridine, sodium, and chloride as well as urine volume and creatinine clearance (N = 5).

	(1)	(2)	(3)
hypoxanthine (μmol/hour)	4.88±2.73	4.94±1.79	4.55±1.61
xanthine (μmol/hour)	3.20±1.85	2.87+1.32	2.82±0.81
uric acid (μmol/hour)	147±30	100±12*	83±15*
uridine (μmol/hour)	0.12±0.04	0.11±0.04	0.11±0.03
urine volume (ml/hour)	227±126	207±79	162±92
creatinine clearance (ml/minute)	107±4	99±13	98±7
sodium (mmol/hour)	7.10±1.64	2.85±1.06**	3.08±1.53**
chloride (mmol/hour)	8.15±2.33	4.85±1.49**	4.88±1.56**

Values are expressed as mean±SD.
(1), (2), and (3): 1 hr before and 1 and 2 hr after, respectively, the administration of octreotide acetate.
* and **: $P<0.05$ and $P<0.01$, respectively, as compared with the value before the administration of octreotide acetate.

below detection limits (2.5 IU/ml) at both 30 and 90 min after (Table 1). However, plasma concentration of cyclic AMP did not change during the study. None of these values changed significantly in the control study (data not shown).

Effect of octreotide acetate on concentrations of lactic acid, pyruvic acid and glucose in blood

Concentrations of lactic acid and pyruvic acid in blood did not change after subcutaneous administration of octreotide acetate (Table 1). However, glucose concentration was decreased by 17% at 30 min after the administration (Table 1). These values did not change in the control study (data not shown).

Effect of octreotide acetate on plasma concentrations of sodium and chloride

Plasma concentrations of sodium and chloride did not change after administration of octreotide acetate in the first study or in the control study (data not shown).

Discussion

In the present study, we found that octreotide acetate decreased the urinary excretion of uric acid as well as the plasma concentrations of glucagon and insulin (Table 1). In addition, octreotide acetate decreased the urinary excretion of sodium and chloride without significant influence on creatinine clearance (Table 2), while the concentrations of lactic acid, pyruvic acid in blood, and cyclic AMP in plasma were not changed (Table 1). The urinary excretion of uric acid is known to be decreased by lactic acid and increased by pyruvic acid [2, 6], and plasma cyclic AMP has been suggested to play a role in hyperuricosuria [21]. However, since the concentrations of lactic acid, pyruvic acid in blood and cyclic AMP in plasma were not changed by octreotide acetate (Table 1), the decreased urinary excretion of uric acid could not be ascribable to those substances. Insulin decreases the urinary excretion of sodium and uric acid in normal subjects and patients with hypertension [12, 13], while insulin-induced changes in urate excretion are coupled to the respective changes in sodium excretion in patients with hypertension [13]. Since octreotide acetate decreased the plasma concentration of insulin in the present study, insulin could not have caused the decrease in urinary excretion of uric acid. Glucagon increases the urinary excretion of uric acid. However, it does not increase that of sodium at the same physiological level as induced by an infusion of 12% amino acid [10]. On the other hand, the urinary excretion of uric acid increases during salt loading and decreases during salt depletion [7], suggesting that the reabsorption of sodium may be coupled with that of uric acid in the kidneys [11–13]. Therefore, we speculated that the octreotide acetate-induced decrease in plasma concentration of glucagon and/or decrease in the urinary excretion of sodium may play a role in the decrease

of urinary uric acid.

We also demonstrated that octreotide acetate increased the plasma concentration of uridine without decrease in urinary excretion of uridine (Tables 1, 2). In addition, octreotide acetate decreased the plasma concentrations of glucagon, insulin and glucose without affecting the plasma concentration of oxypurines. Abrupt ATP consumption enhances pyrimidine degradation (UDP→UMP→uridine), resulting in an increase in plasma concentration of uridine [18-20]. However, in the present study, octreotide acetate did not change the plasma concentrations or urinary excretion of hypoxanthine and xanthine (Tables 1, 2), indicating that purine degradation was not affected. Glucose intake of caused a transient increase in plasma concentration of uridine, without changing the plasma concentration and urinary excretion of purine bases (hypoxanthine, xanthine, and uric acid) by enhancing glycogenesis, leading to a presumable abrupt consumption of UDP-glucose, an increase in UDP, and then UDP degradation (UDP→UMP→uridine) [17]. However, since blood glucose was not increased in the present study, an octreotide-induced increase in plasma concentration of uridine cannot be ascribable to a change in blood glucose. Insulin and glucagon enhance uridine uptake into cells via the Na-dependent nucleoside transport pathway *in vitro* [16], while glucagon decreases the plasma concentration of uridine *in vivo*, by presumably promoting the uptake of uridine via the Na-dependent nucleoside transport pathway [10]. Therefore, it is speculated that the octreotide acetate-induced decrease in plasma concentrations of glucagon and insulin observed here may have a relationship with increase in plasma uridine concentration without decreasing its level of urinary excretion.

Octreotide acetate is used to treat patients with acromegaly and giantism [22], because it inhibits the secretion of growth hormone from pituitary adenoma and possesses a long biological half-life (100 min). However, it has not been reported that octreotide acetate develops hyperuricemia in these patients. Therefore, the effect of octreotide acetate on the urinary excretion of uric acid may not be clinically important. On the other hand, since the physiological action of plasma uridine in humans remains undetermined as does the role octreotide acetate plays in nucleoside metabolism by increasing the plasma concentration of uridine, further investigation is needed.

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