Effects of Thyroxine on Hyperkalemia and Renal Cortical Na⁺, K⁺-ATPase Activity Induced by Cyclosporin A

Cyclosporin A (CsA)-induced hyperkalemia is caused by alterations in trans-epithelial K⁺ secretion resulting from the inhibition of renal tubular Na⁺, K⁺-ATPase activity. Thyroxine enhances renal cortical Na⁺, K⁺-ATPase activity. This study investigated the effect of thyroxine on CsA-induced hyperkalemia. Sprague-Dawley rats were treated with either CsA, thyroxine, CsA and thyroxine, or olive-oil vehicle. CsA resulted in an increase in BUN and serum K⁺, along with a decrease in creatinine clearance, fractional excretion of potassium, and renal cortical Na⁺, K⁺-ATPase activity, as compared with oil vehicle administration. Histochemical study showed reduced Na⁺, K⁺-ATPase activity in the proximal tubular epithelial cells of the CsA-treated compared with the oil-treated rats. Histologically, isometric intracytoplasmic vacuolation, disruption of the arrangement and swelling of the mitochondria, and a large number of lysosomes in the tubular epithelium were characteristic of the CsA-treated rats. Co-administration of thyroxine prevented CsA-induced hyperkalemia and reduced creatinine clearance, Na⁺, K⁺-ATPase activity, and severity of the histologic changes in the renal tubular cells when compared with the CsA-treated rats. Thyroxine increased the fractional excretion of potassium via the preservation of Na⁺, K⁺-ATPase activity in the renal tubular cells. Thus, the beneficial effects of thyroxine may be suited to treatment modalities for CsA-induced hyperkalemia.

Key Words : *Cyclosporin A, Hyperkalemia, Thyroxine, Renal Corex; Na⁺,K⁺-ATPase*

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INTRODUCTION

Although cyclosporin A (CsA) has been hailed as a major advance in transplantation, increasing both graft and patient survival, its use is sometimes limited by nephrotoxicity and hyperkalemia which have been commonly observed in renal transplant patients successfully treated with cyclosporine (1, 2). The pathogenesis of CsA-induced nephrotoxicity remains unclear. Intrarenal vasoconstriction at the level of the afferent glomerular arteriole is at the cornerstone of the pathogenesis (3, 4), but its mechanism has not been fully elucidated.

Another common complication of CsA-treatment is hyperkalemia. Formerly, several reports have suggested that the development of hyperkalemia is specifically associated with the therapeutic administration of CsA, and it was believed that the mechanism of hyperkalemia involved the reduction of potassium secretion as a result of renal tubular damage and hypoaldosteronism (2, 5). But recently, Suzuki et al. (6) reported that prolonged use of CsA suppresses DNA and RNA synthesis, as well as Na⁺, K⁺-ATPase activity in the renal cortex and subsequently damages the tubular basement membrane resulting in nephrotoxicity and hyperkalemia. This finding has been confirmed by Ihara et al. (7), Tumlin et al. (8), and Anderson et al. (9) in experiments with rodents.

Thyroxine administration has shown protective effects in several experimental models of acute renal failure induced by various and numerous nephrotoxic agents. These effects have been associated with a rise of Na⁺, K⁺-ATPase activity in the basolateral membranes of renal tubules (10-14).

We designed the present experiment to examine the protective effects of thyroxine on CsA nephrotoxicity and hyperkalemia by comparing the Na⁺, K⁺-ATPase activity in renal tubular cells and the level of potassium.

MATERIALS AND METHODS

Drugs

CsA (Sandimmune, Sandoz Co, Swiss) and L-thyroxine (Sigma Chemical, St. Louis, MO, U.S.A.) were used for the study. The thyroxine was dissolved in 0.01 N NaOH to a concentration of 100 g/mL and stored at 20°C before used.

Experimental protocol

Twenty-six pathogen-free, male, Sprague-Dawley rats weighing 200-230 g were assigned to one of the following

four groups of treatment: group 1 (N=5), olive-oil vehicle; group 2 (N=7), thyroxine (25 μg/kg) subcutaneously; group 3 (N=7), CsA (25 mg/kg) intraperitoneal injection; group 4 (N=7), thyroxine (25 μg/kg) subcutaneous injection followed by CsA (25 mg/kg) intraperitoneal injection one hour later. All studies were carried out for 30 days and all rats were pair-fed using tap water and standard rat chow to control effects of cyclosporine-induced weight loss. The dose of thyroxine (25 μg/kg) used in this experiment was 20- to 320-fold lower than those used in previous experiments to study hyperthy-roidism in this species (15).

Measurement of physiologic and blood chemistry data

The following measurements, including body weight, were taken before initiation of therapy and immediately prior to sacrifice after 30 days of drug administration. The systolic blood pressures (SBP, means of three measurements) were measured in unanesthetized rats by plethysmography with a rat tail manometer-tachometer system (Natsume Seisakusho Co. Ltd., Tokyo, Japan). The serum collected for BUN, creatinine concentration, and creatinine clearance was analyzed by a Hitachi 747 autoanalyzer (Hitachi Co. Japan). Creatinine clearance was calculated by a standard formula. The serum concentration of potassium and fractional excretion of potassium (FE$_K$) were analyzed by an Atra-8 autoanalyzer (Beckman Co. Palo Alto, CA, U.S.A.). In the rats receiving CsA, the trough concentrations of the drug were measured on day 30 by fluorescence polarization immunoassay (TDX, Abbott Lab., Abbott Park, IL, U.S.A.) using whole blood.

On day 30, the rats were anesthetized with an intraperitoneal injection of pentobarbital at a dose of 30-50 mg/kg, and the kidney was exposed with a midline incision and stripped of its capsule. After 3-5 mL of blood had been obtained from the descending aorta, this vessel was ligated just above the origin of the renal artery. The kidney was emptied of blood by perfusion (250 mM sucrose, 10 mM HEPES buffer, 0.5 mM EDTA) using a catheter, and the organs were removed and sliced into 0.5- to 1-mm sections in dishes resting on ice. The cortex was dissected out, placed on filter paper, and weighed after removing water on the surface. Serum was separated from the blood sample and stored at -20°C until assayed. Renal function markers and electrolyte concentrations were measured within 5 days.

Separation of microsomal fraction in renal cortex tissue

The microsomal fraction was obtained using a modification of the Jørgensen and Skou's method (16). Perfusion solution was added to the renal cortical tissue (20 mL/g), and the tissue was homogenized by 10 strokes in a glass homogenizer with a Teflon pestle at 1,500 rpm. The homogenate was centrifuged at 1,300 g for 10 min at 4°C in a Beckman J2-MC refrigerated centrifuge. The supernatant fluid was saved, and

the pellet was resuspended in half the original volume of sucrose buffer and centrifuged as above for 10 min at 1,300 g. The supernatant fluid was decanted and combined with the previous supernatant material (Fraction 1). Fraction 1 was centrifuged at 9,500 g for 15 min, and the resulting supernatant fluid and the fluffy layer of the pellet were removed by a Pasteur pipette and pooled as Fraction 2. Fraction 2 was centrifuged at 25,000 g for 30 min. The supernatant fluid and the dark lower pellet were discarded, and the upper fluffy pellet was resuspended in sucrose buffer. This fraction (Fraction 3) contained the microsomes and was stored at -70°C, either for later measurement of enzyme activity or for immediate use. The protein concentration was measured by the method of Lowry et al. (17) using bovine serum albumin as a standard after the tissue preparations had been adjusted to a protein concentration of 1 m/L.

Measurement of Na$^+$, K$^+$-ATPase in kidney tissues

The Na$^+$, K$^+$-ATPase activity was measured by the Jørgensen and Skou's method (16). Microsomal-fraction protein (150 μg in 600 μL of a solution consisting of 12.5 mM imidazole and 1 mM EDTA) was incubated at 25°C for 30 min, and the enzyme activity was measured by determining the amount of inorganic phosphate liberated from ATP in 1 mL of a solution containing 130 mM NaCl, 20 mM ATP, 3 mM MgCl$_2$, 30 mM L-histidine, 10 mM HEPES buffer (pH 7.5), and 25 μL of microsomal-fraction protein. The solution (100 μL) was mixed with 0.8 mL of buffer solution for measurement of total ATPase and Mg^{2+}-ATPase. The ATPase reaction was initiated by the addition of 100 μL of 3 mM ATP after a 10-min equilibration in a 37°C waterbath. The reaction was carried out in the presence or absence of 1 mM ouabain and terminated with 0.3 mL of 6% perchloric acid. The solution was centrifuged at 2,000 g for 15 min at 4°C, and the amount of Pi was measured at 660 nm in a spectrophotometer using the Fiske and Subbarow method (18). The enzyme activity suppressed by the addition of ouabain was considered equivalent to the activity of Na$^+$, K$^+$-ATPase and was expressed as mole Pi/mg of protein per hour.

Detection of the distribution of Na$^+$, K$^+$-ATPase in kidney tissues by histochemistry

The distribution of Na$^+$, K$^+$-ATPase in kidney tissues was determined using a modification of the method of Mayahara et al. (19). The renal cortical tissue was perfused with solution containing 2% polyvinyl pyrrolidone, 0.8 mM CaCl$_2$, and 100 mM histidine (pH 7.25) with 0.1 M KOH for 15 to 20 min and then refrigerated at -60°C with dry ice-acetone. After placement in N-methylbutane for 2 to 5 min, the tissue was frozen at -20°C. Frozen sections in 5 to 24 μm thickness were cut and then dried at room temperature for 15 to 20 min. The dried tissue was incubated in a 20 mL

solution consisting of 30 mM KCl, 5 mM MgCl$_2$, 5 mM β-nitrophenylphosphate, and 70 mM 2-amino-2-methyl-1-propanol buffer (pH 9.0) with the addition of 1 mM ouabain at 37°C for 1 to 3 hr and then placed in 2% CoCl$_2$ for 5 min. The tissue was then rinsed with distilled water, washed with 2-amino-2-methyl-1-propanol buffer (79 mM; pH 9.0) three times for 30 sec each, placed in light ammonium sulfide (diluted 1:50 v/v) for 3 min, and rinsed again in distilled water. The specimens were then dried with alcohol and xylene and fixed for light microscopic examination.

Histopathology of kidney tissues

Light microscopic analysis was made on periodic acid-Schiff (PAS) stained thin kidney sections. For electron microscopy, tissues were prefixed in 0.5% glutaraldehyde, postfixed in 1% osmium tetroxide, dehydrated in a graded alcohol series and propylene oxide, and embedded in a Epon mixture solution. Thin sections were cut with a diamond knife, stained with uranyl acetate on a 100-mesh grid, and examined with a Hitachi HS-9 electron microscope at 75 kV.

Statistical analysis

The results were expressed as mean±SE. Statistical significance was determined by the Wilcoxon rank sum test, with a p value of less than 0.05 being considered significant.

RESULTS

Body weight and blood pressure data

The experimental technique of pair feeding controlled to a relatively effective degree for cyclosporine-induced reduction of dietary intake. There were no significant differences in the final body weights at sacrifice among the experimental rats over the 30 days of our study, except the CsA-treated rats which gained 8 g, and the oil-treated rats which gained 33 g. CsA treatment alone resulted in a slight but not significant elevation in SBP, as compared with the oil-treated rats. There was no significant difference in body weight among any of the four groups (Table 1).

Blood chemistry data

Intergroup comparison on day 30 showed a two-fold increase of the BUN concentration in the CsA-treated rats, compared with the oil-treated rats (46.4±5.3 vs 20.5±4.2 mg/L, $p<0.05$). Serum creatinine concentrations in the CsA-treated rats also rose significantly compared with both the oil-treated rats and thyroxine-treated rats (1.0±0.3 vs. 0.7±0.2 and vs. 0.5±0.2 mg/dL, respectively, $p<0.05$). Creatinine clearance was significantly lower in the CsA-treated rats (3.8±1.1 L/mg day $p<0.05$) and lower, although not significantly, in the CsA+thyroxine-treated rats (5.4±1.6 L/mg day, $p<$NS) than in the oil-treated rats (6.2±2.4 L/mg day) (Table 2). Administration of thyroxine alone had no effect on BUN, serum creatinine, or creatinine clearance. No significant difference in the serum CsA level was observed in the CsA-treated and CsA+thyroxine-treated rats (2.954±1.003 vs 3.126 ±1.362 ng/mL).

Serum potassium and fractional excretion of potassium (FE$_K$)

The serum potassium concentration was higher in the CsA-treated rats than in oil-treated rats (5.2 vs 4.5 mEq/L, $p<0.05$), but showed no significant difference among the oil-treated, thyroxine-treated, and CsA+thyroxine-treated rats (Fig. 1). The FE$_K$ value was significantly lower in the CsA-treated rats than in the oil-treated rats (40±15.1 vs 61.2±2.4%, $p<0.05$). No significant difference in the FE$_K$ value was observed between the thyroxine-treated and oil-treated rats (Fig. 2). Hyperkalemia was found to correlate with the FE$_K$ value in the CsA-treated rats.

Na$^+$, K$^+$-ATPase activity in the renal cortical microsomal fraction

Na$^+$, K$^+$-ATPase activity was significantly lower in the CsA-treated rats than in the oil-treated rats (37.5±6.5 vs 17.5 ±7.7 mole pi/mg protein/hr, $p<0.05$) (Fig. 3), whereas no significant difference was observed between the oil-treated

Table 1. Changes in body weight and systolic blood pressure from initial to final measurement in study groups

Groups	Body weight (g)		Systolic blood pressure (mmHg)	
	Initial	Final	Initial	Final
Oil (N=5)	215.4±7.3	248.3±9.4	92.7±17.4	95.0±5.0
Thyroxine (N=7)	207.7±9.2	228.5±6.6	89.4±9.4	90.4±7.3
CsA (N=7)	224.6±6.2	232.3±5.5	90.5±10.5	95.0±16.4
CsA+Thyroxine (N=7)	213.3±5.7	236.4±4.7	94.6±12.3	96.6±9.5

Values are expressed as mean±SE. CsA: cyclosporin A.

Table 2. Effect of thyroxine on glomerular function and cyclosporine blood level

Groups	BUN (mg/L)	Creatinine (mg/dL)	Ccr (L/mg day)	CsA blood level (ng/mL)
Oil (N=5)	20.5±4.2	0.7±0.2	6.2±2.4	-
Thyroxine (N=7)	22.4±5.2	0.5±0.2	5.8±1.9	-
CsA (N=7)	46.4±5.3*	1.0±0.3	3.8±1.1*	2,954±1,003
CsA+Thyroxine (N=7)	24.9±2.7	0.6±0.3	5.4±1.6	3,126±1,362

Values are expressed as mean±SE. BUN, blood urea nitrogen; Ccr, creatinine clearance; CsA, cyclosporin A. *$p<0.05$ compared with oil.
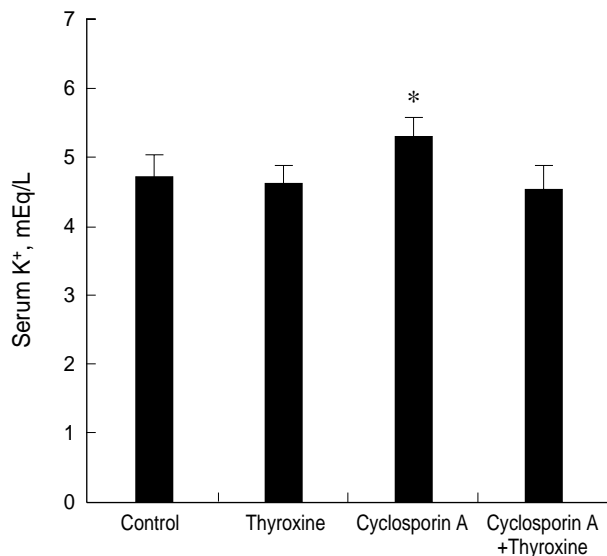
Fig. 1. Serum potassium levels in study groups after 30 days of thyroxine, cyclosporin A, and cyclosporin A+thyroxine administration. *$p<0.05$: compared with control.

Fig. 2. Fractional excretion of potassium (FE$_K$) in study groups after 30 days of thyroxine, cyclosporin A, and cyclosporin A+ thyroxine administration. *$p<0.05$: compared with control.

and CsA+thyroxine-treated rats.

Histochemical staining of Na⁺, K⁺-ATPase in the kidney

The staining extent was determined by the relative abundance of different nephron segments in each zone including outer medulla, cortex, and inner medullary papilla. The greatest degree of staining was detected in the thick ascending loop of Henle in the outer medulla and distal convoluted tubule in both oil and thyroxine-treated rats. The enzymatic reaction was markedly reduced in the proximal tubules of CsA-treated rats compared with the oil-treated rats, but there was no significant difference between the oil-treated rats and CsA+thyroxine-treated (Fig. 4).

Histopathologic effect of thyroxine in CsA-treated rat kidney

Light microscopically, no morphological changes were noted either in the kidneys treated with oil or those with thyroxine alone. In the CsA-treated rat kidneys, morphological changes were noted along the entire length of the proximal tubules. The light microscopic alterations were confined to the thick ascending loop of Henle at the cortico-medullary junction, and consisted of cytoplasmic swelling, cytoplasmic vacuolation of varying degrees, and small PAS-positive granules. Frank cell necrosis was not present. In some areas, all the cells lining a tubule were affected, while in others only alternate or fewer cells were involved. The vacuolation varied from fine sub-nuclear cytoplasmic stippling to large vacuoles measuring up to 5 μm in diameter. Although these findings were also noted in the CsA+thyroxine-treated rat kidneys, the tubular epithelial cytoplasmic swelling was milder with
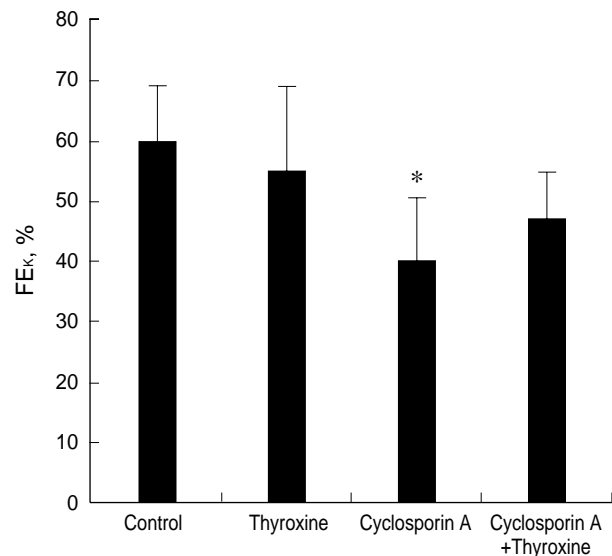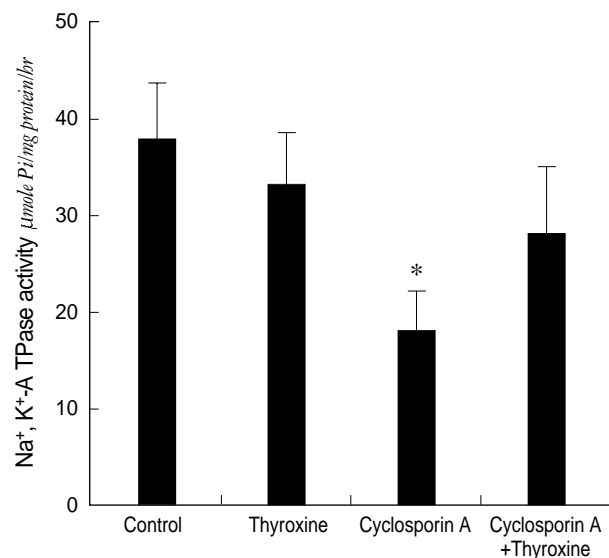

Fig. 3. Renal cortical Na⁺, K⁺-ATPase activities in study groups after 30 days of thyroxine, cyclosporin A, and cyclosporin A+ thyroxine administration. *$p<0.05$: compared with control.

fewer cytoplasmic granules in this group than in the CsA-treated ones (Fig. 5). Electron microscopically, no morphological changes were noted in cells of the renal corpuscle from the oil and thyroxine-treated rats. The localized proximal tubular cytoplasmic vacuolation visible on light microscopy was due to dilatation of the endoplasmic reticulum. Both smooth and rough endoplasmic reticulum were affected. The small PAS-positive granules found in the CsA-treated and CsA+thyroxine-treated rat kidneys were primary and secondary lysosomes in the proximal tubular epithelial cells. Furthermore, disruption of arrangement including variation of the size and shortening of the cristae, along with swelling
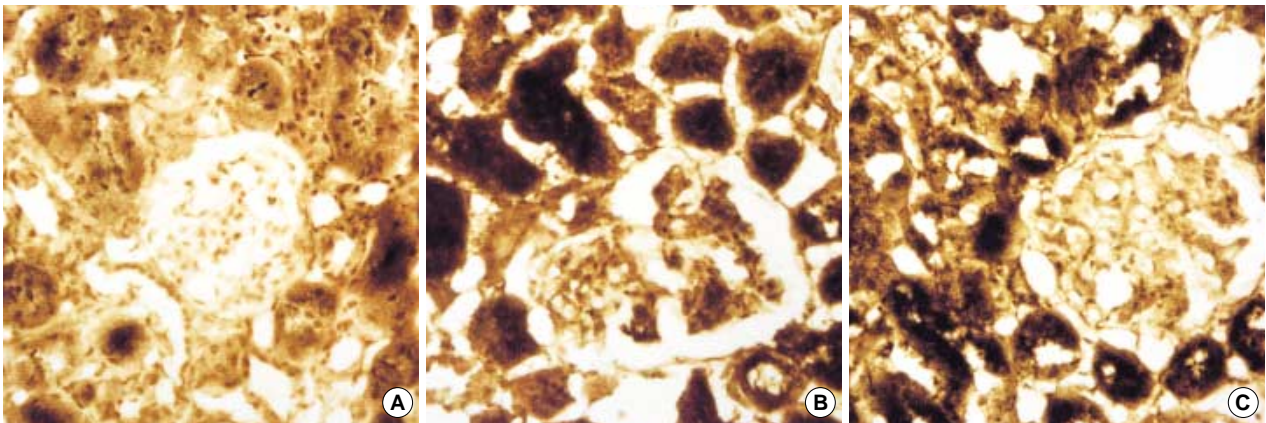
Fig. 4. Na$^+$, K$^+$-ATPase reaction of the proximal tubular epithelial cells by using frozen tissue section is remarkably reduced in cyclosporin A administered group (**A**) compared to normal control (**B**). Reduction of Na$^+$, K$^+$-ATPase reaction is partly protected when cyclosporin A was administered with thyroxine (**C**).
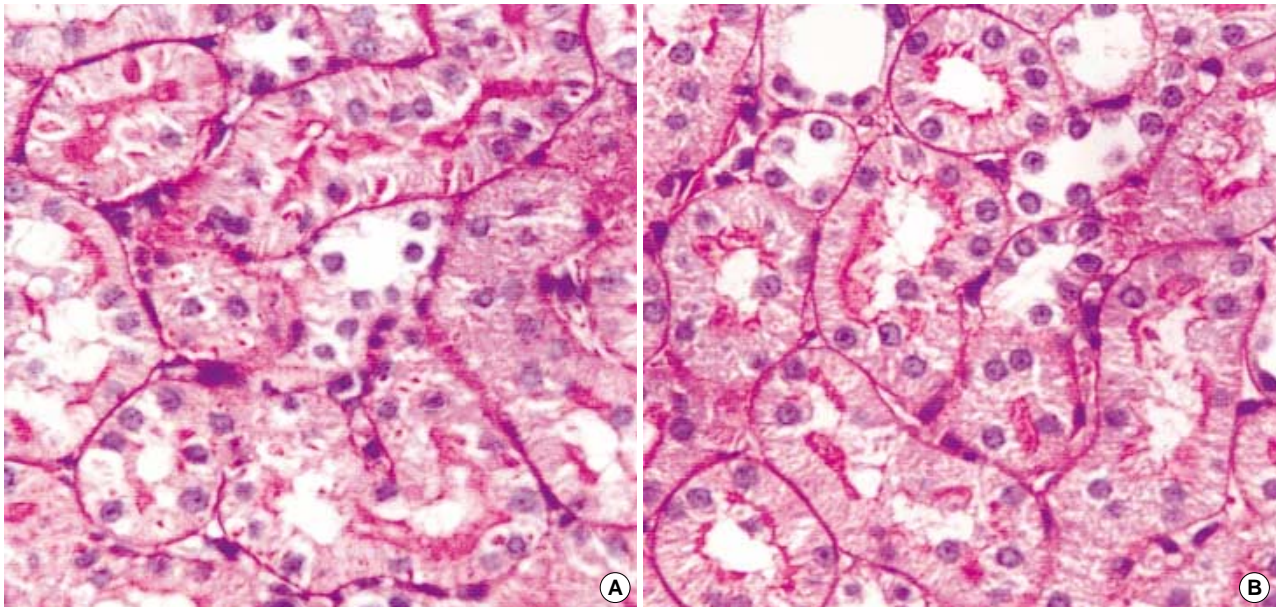

Fig. 5. Presence of small cytoplasmic hyaline globules in proximal tubular cells in addition to cytoplasmic edema is a characteristic finding of cyclosporin A administered group (**A**). These findings are attenuated in number when thyroxine is added although cytoplasmic edema is still noted.

of the mitochondria, was also found. Light microscopic findings of the CsA+thyroxine-treated rats indicated a marked reduction in the number of lysosomes and disruption of the mitochondria (Fig. 6).

DISCUSSION

Anderson et al. (9) reported that an increase in lysophosphatidyl choline, generated by inhibition of Na$^+$, K$^+$-ATPase activity during CsA treatment of mitogen- or antigen-activated lymphocytes, represented a possible mechanism for the immunosuppressive activity of CsA. Moreover, the decrease

in Na$^+$, K$^+$-ATPase is secondary to a change in the arachidonic acid metabolism or in the binding of CsA and the alpha subunit of the enzyme. These findings suggest that the immunosuppressive effect of CsA may result from its suppression of Na$^+$, K$^+$-ATPase activity in lymphocytes.

Also, Ihara et al. (7) found that potassium release from human erythrocytes after CsA treatment is attributable mainly to the activation of the K$^+$channel and partial inhibition of Na$^+$, K$^+$-ATPase by CsA, suggesting that the K$^+$ efflux might be one of the underlying mechanisms of hyperkalemia. Adu et al. (5) reported that the etiologic factors of hyperkalemia and hyperchloremic acidosis could be caused by hypoaldosteronism or renal tubular resistance to the action of aldos-
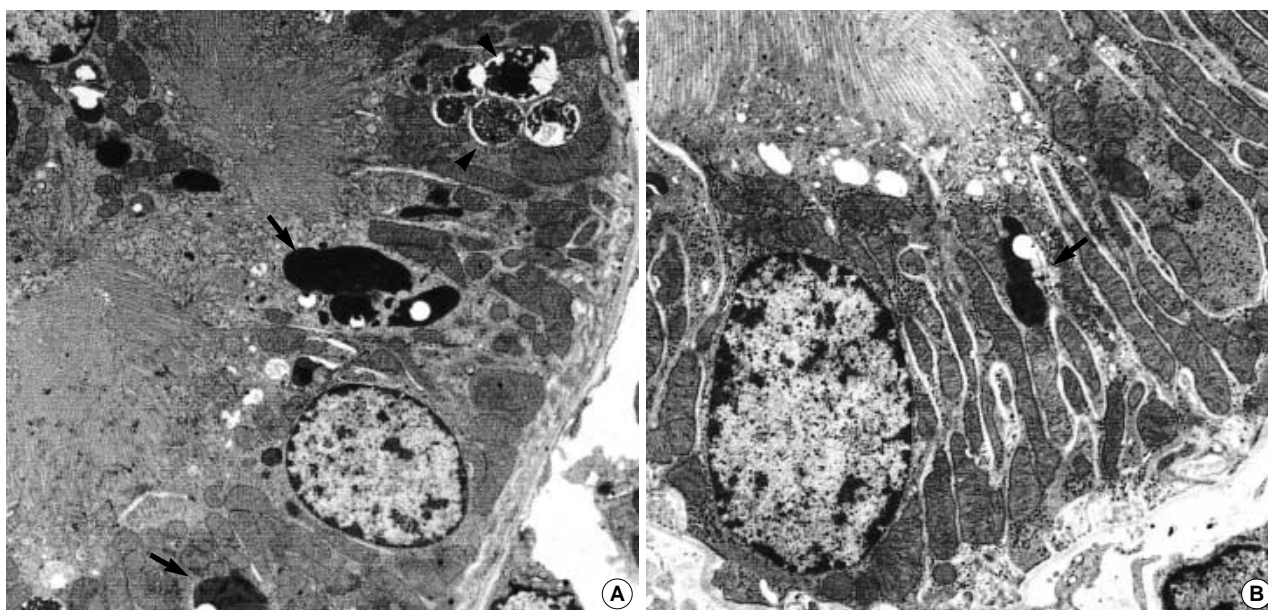
Fig. 6. Ultrastructurally, cytoplasmic hyaline globules in light microscopy are proved as primary (arrows) and secondary (arrow heads) lysosome (cyclosporine group: A). These are decreased in number in the thyroxine+cyclosporin A administered group.

terone or renal tubular damage leading to a tubular defect of potassium and hydrogen secretion. Tumlin and Sands (8) reported that the cause of CsA-induced hyperkalemia is not hypoaldosteronism but rather a direct result of the inhibition of Na$^+$, K$^+$-ATPase in the renal tubule.

Na$^+$, K$^+$-ATPase is an integral membrane protein present in all mammalian cells. By actively pumping sodium ions out of cells and potassium ions into cells, the enzyme generates a sodium ion gradient that is used by the cell to run a variety of secondary Na$^+$-dependent transport reactions. Glucose, amino acids, and essential ions such as hydrogen and phosphates are moved across the cell membrane by these carriers. Thus, Na$^+$, K$^+$-ATPase is a key enzyme for cellular homeostasis. When its function is reduced or lost, cellular swelling and death occur (20). Potential factors involved in the regulation of Na$^+$, K$^+$-ATPase are the supply of sodium, potassium, phosphate ions, and a number of hormones including chiefly adrenal corticosteroids, thyroid hormones, and perhaps insulin.

We investigated in this study whether exogenous thyroxine decreased nephrotoxicity and hyperkalemia in CsA-treated rats by physiologic and histologic investigation, biochemical measurements and determination of Na$^+$, K$^+$-ATPase activity in thin kidney sections. The data from this study demonstrate the prevention/reduction of CsA-induced nephrotoxicity and hyperkalemia by exogenous thyroxine in vivo, as evidenced by histopathologic changes and Na$^+$, K$^+$-ATPase activity in renal tissues. Our findings suggest that a potential mechanism for CsA-induced hyperkalemia and nephrotoxicity may be related to the tubular structural damage which results from the inhibition of tubular Na$^+$, K$^+$-ATPase activity, and

that this damage is attenuated by exogenous thyroxine.

Thyroxine has been shown to play a afforded protective role and stimulate Na$^+$, K$^+$-ATPase activity in experimental models of acute renal failure, but the dose and time of administration differed among the models. The influence of thyroxine on normal renal function is well documented; as depressing the glomerular filtration rate below normal in hypothyroidism, whereas increasing it above normal in hyperthyroidism. However, it is unlikely that the protection provided by thyroxine in the present study was due to the induction of a hyperthyroid state. The dose used in this study of 25 μg/kg body weight is 20- to 320-fold lower than those used in previous studies on hyperthyroidism in rats. Furthermore, thyroxine alone had no effect on renal hemodynamics, as demonstrated by the stable physiologic and blood chemistry data (11).

CsA nephrotoxicity is manifested histologically as tubular damage (6, 21, 22). The demonstration by Suzuki et al. (6) of the relief of histologic damage and hyperkalemia by glucocorticoid treatment suggests that the mechanism involves stimulation of renal tubular Na$^+$, K$^+$-ATPase and gives support to the hypothesis that the adverse effects of CsA are indeed the result of a decrease in the activity of this enzyme. In our study of CsA-induced nephrotoxicity and its prevention, we used thyroxine, which is more effective than glucocorticoids in preventing many kinds of renal toxicity (10-14). Accurate measurement of Na$^+$, K$^+$-ATPase activity in the mi-crosomal fraction is time-consuming and demanding, so we also used a histochemical approach for the measurement of the enzyme activity. The usefulness of the latter method was confirmed by its indication of markedly reduced Na$^+$, K$^+$-ATPase activity in the CsA-treated rats.

Our finding of a lesser degree of histologic damage in the rats receiving thyroxine suggests that the renal damage caused by CsA is the result of inhibition of Na^+, K^+-ATPase. According to Tumlin and Sands (8), the reduction of Na^+, K^+-ATPase activity is detectable within 30 min after CsA administration, even before the histologic change becomes apparent. Thus, the inhibitory effect appears to be a direct action, as opposed to a secondary effect. As a result of the inhibition, an abnormal Na^+-gradient across the cell membrane arises, leading to a disturbance of cellular homeostasis, and finally, to histologically visible renal damage. Hyperkalemia also results from the inhibition of this enzyme, although the exact mechanism is not known.

These biochemical changes are accompanied by structural damage, affecting the straight segment of the renal proximal tubule. The presence of increased numbers of lysosomes throughout the proximal convoluted tubule indicates sublethal cellular damage and is reflected in the increased level of serum creatinine and decreased creatinine clearance. This structural damage observed in the thick descending limb of the loop of Henle is consistent with such an impairment of sodium reabsorption from the tubule.

Cronin et al. (13) showed that both the number and size of lysosomes were decreased when thyroxine was used to prevent gentamicin nephrotoxicity. They suggested that the mechanism of thyroxine's protective effect involved the reduction of drug uptake by pinocytosis and was related to increased Na^+, K^+-ATPase activity. In our study on long-term CsA (25 mg/kg for 30 days) administration, the kidney demonstrated cytoplasmic vacuolation in proximal tubular epithelial cells and deposition of lysosomes which were confirmed by light and electron microscopy, although our experimental rats did not receive the large CsA doses (50 or 100 mg/kg for 21 days) employed by Whiting et al. (21), nor a salt-restricted diet. This change was attenuated by exogenous thyroxine, which averted the reduction of Na^+, K^+-ATPase activity. Also, the number of lysosomes was increased by CsA administration and decreased by thyroxine co-administration. It is probable that the decreased Na^+, K^+-ATPase activity and increased number of lysosomes are related events, however, because the amount of CsA in the lysosomes was not measured, it is not clear whether thyroxine's protective effect resulted from the reduction of the amount of nephrotoxic material influx into the renal tubular cells or from the increased Na^+, K^+-ATPase activity. To date, hyperkalemia has easily been managed by cation exchange resins and CsA may be used in other medical conditions than organ transplantation. So we recommend that the serum concentration of potassium be carefully monitored when CsA is administered to patients with conditions associated with impaired potassium metabolism or to those receiving other drugs that influence the disposition of potassium (3).

In conclusion, our study demonstrates that CsA-induced hyperkalemia is associated with decreased Na^+, K^+-ATPase activity and increased lysosomal levels, and that thyroxine treatment attenuates this reduction of Na^+, K^+-ATPase activity. The administration of thyroxine may be useful in controlling CsA-mediated hyperkalemia. Further studies measuring the amount of CsA in the lysosomes are necessary to elucidate the thyroxine protection mechanism.

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