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Renal Handling of Sodium and Potassium in Cadmium Exposed Rats

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Effects of cadmium exposure on renal Na^+ and K^+ transports were studied in rats. During the course of cadmium treatment (2 mg Cd/kg/day, s.c. injections for 3 weeks) renal tubular transports of Na^+ and K^+ were evaluated by lithium clearance technique. During the early phase (first week) of cadmium treatment, urinary Na^+ excretion decreased drastically and this was due to an increased Na^+ reabsorption both in the proximal and distal nephrons. During the late phase (third week) of cadmium treatment, filtered Na^+ load was decreased by reduction in GFR, but the renal Na^+ excretion returned to the control level due to impaired Na^+ transport in the proximal tubule. Urinary excretion of K^+ did not change during the early phase, but it rose markedly during the late phase of cadmium treatment. These results indicate that a light cadmium intoxication induces a Na^+ retention, and a heavy intoxication results in a K^+ loss. Possible mechanisms for these changes are discussed.

Key Words: Cadmium, Renal function, Na^+ excretion, K^+ excretion, Lithium clearance

INTRODUCTION

It has been widely documented in humans (Flick et al, 1971; Kazantzis, 1978; Kjellstrom & Nordberg, 1978; Bernard et al, 1979; Lauwerys et al, 1979) and experimental animals (Axelson & Piscator, 1966, Perry & Erlanger, 1971; Nordberg & Piscator, 1972; Foulkes, 1974; Bernard et al, 1981; Goon & Klaassen, 1989, Goyer et al, 1989) that chronic exposures to cadmium result in various nephrotoxicities. This is because the cadmium ingested is eventually brought to the kidney and accumulates in the proximal tubular cell (Kjellstrom, 1986). The cadmium ingested is initially sequestered by the liver and bound to metallothionein (a cystein-rich apoprotein, M.W. about 6500 daltons). The cadmium-metalothionein complex released into the circulation is filtered through glomerulus and is taken up by the proximal tubular cell by the transport mechanism for low molecular weight proteins (i.e., endocytosis). The complex is rapidly degraded in the lysosome, liberating free cadmium ion which, in turn, induces tubular cell injury (Squib et al, 1982). The critical concentration of cadmium for renal toxicity is reported to be approximately 200 μg per gram of renal cortex (Kazantzis, 1979).

Cadmium-induced renal dysfunction is characterized by proteinuria, glycosuria, aminoaciduria, phosphaturia, hypercalciuria, polyuria, and hyposthenuria (see Kim et al, 1988 for Ref). Under normal conditions, filtered glucose, amino acids, phosphate, and calcium are mostly reabsorbed in the proximal tubule by processes associated with Na^+ reabsorption. Thus, an increase in their urinary excretion may imply a decrease in proximal tubular Na^+ reabsorption. However, several studies in cadmium-exposed animals (Lener & Musil, 1970; Perry et al, 1971; Friberg et al, 1974; Porter et al, 1974; Doyle et al, 1975) revealed that the urinary excretion of Na^+ does not change or even decreases sometimes. Perry et al (1971) have observed Na^+ retention in long-term (52 weeks) cadmium exposed rats. Vander (1962) and Dolye et al (1975) observed Na^+ and water retention in acutely cadmium-exposed dogs and rats, respectively. It is not clear how the Na^+ and fluid retention is occurred by cadmium exposure.

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We, therefore, carried out several series of experiment on rats to investigate the effect of cadmium exposure on the renal Na^+ handling. During the course of cadmium exposure (2 mg Cd/kg/day s.c. injections for 2~4 weeks) changes in renal Na^+ and K^+ excretions were evaluated. The first series of experiment (Kim et al, 1988) showed that a short-term (for 4~7 days) exposure to cadmium induced Na^+ retention with no changes in K^+ excretion, whereas a long-term (more than 2 weeks) exposure resulted in marked kaliuresis with or without significant natriuresis. The excretions of other solutes, such as glucose, phosphate and calcium, were not changed after a short-term exposure, but they increased markedly after a long-term exposure. These were confirmed in another series of experiment (Kim & Park, 1989) which also showed that the renal cortical Na^+-K^+-ATPase activity was increased by a short-term cadmium exposure and decreased by a long-term exposure. Such results suggest that the Na^+ transport in the proximal tubule is activated in light cadmium intoxication, but inhibited in heavy intoxication. We evaluated this possibility in the present study by determining the Na^+ transport in the proximal tubule and distal nephron using lithium clearance technique (Thomsen & Schou, 1986).

METHODS

Animals

Male Sprague-Dawley rats (200~300 g) were maintained, unless otherwise mandated by experimental protocol, under standard laboratory condition with *ad libitum* access to food and water. After determining the baseline renal function, the experimental group received a daily subcutaneous injection dose of 2 mg Cd ($CdCl_2$ dissolved in saline) per kg body weight over 3 weeks. The control group received the same volume of plain saline.

Determination of renal functions

Renal functions were determined at 1-week intervals. Animals were kept in metabolic cages and were denied food and water for 24 hours. When lithium clearance was measured, 10~15 mM LiCl solution was given as drinking water for 2~3 days prior to urine collection. The initial concentration of lithium in the plasma was maintained below 0.5 mEq/l to prevent adverse effects of high concentration of lithium on renal function (Foulkes et al, 1952; Thomsen & Schou, 1968). Urine was collected under a film of mineral oil in a glass cylinder in order to prevent evaporation. Blood samples were taken from the tail or heart immediately before and after each urine collection and plasma was immediately separated by a microcentrifuge. The urine and plasma samples were analyzed for Na^+/K^+ (Radiometer Flame Photometer, Model FLM 3, Copenhagen, Denmark), Li^+ (Hitachi Atomic Absorption Spectrophotometer, Model 180-30, Tokyo, Japan), creatinine (Wako Technical Bulletin No. 271-10509, Wako Pure

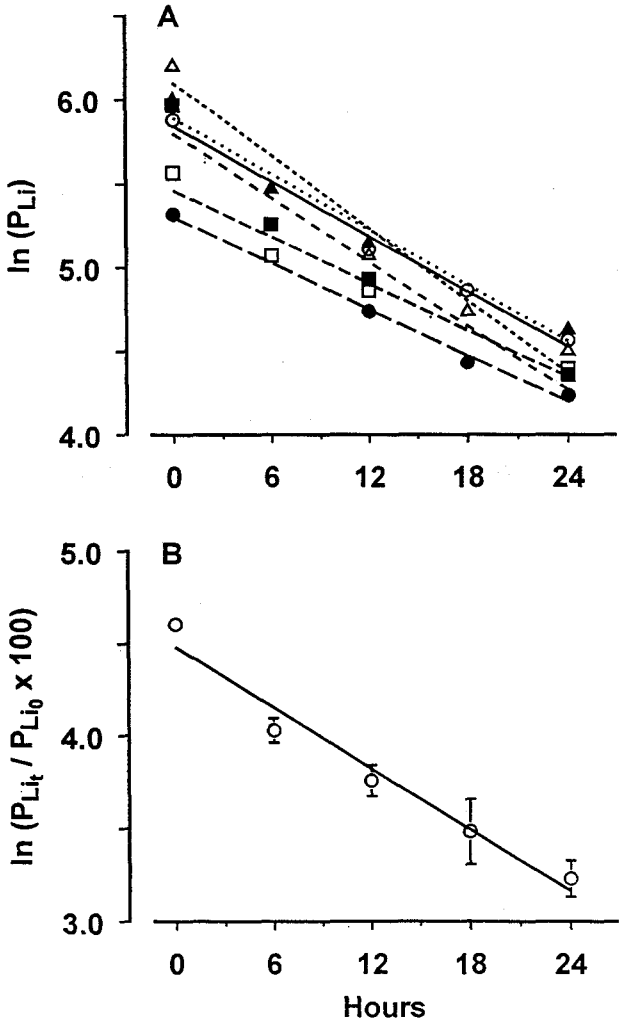

Fig. 1. Changes in plasma lithium concentration. Individual logarithmic values of the plasma lithium concentration (mM) in 6 rats (A) and the average values± S.E. normalized with the initial concentration (B) were plotted as a function of time.

Chem. Ind., Osaka, Japan) and osmolality (Advanced Digimatic Osmometer, Model 3D2, Needham Heights, MA, USA).

For the lithium clearance, a preliminary study was performed to evaluate changes in plasma lithium concentration during the urine collection period. Fig. 1A depicts individual logarithmic values of plasma lithium concentration in 6 rats at 6-hour intervals and Fig. 1B represents the average normalized value. The plasma lithium concentration decreased exponentially during a 24-hour period according to the following equation:

$$\ln P_{Li_t} = \ln P_{Li_0} - k\ t$$

where, P_{Li_0} and P_{Li_t} are the plasma lithium concentration at initial and an arbitrary time, k is the exponential rate constant (slope = 0.0556/h) and t is the experimental time. Thus, in actual experiments, the average plasma lithium concentration during urine collection period was assessed by the above equation using the plasma lithium levels immediately before and after urine collection.

The clearance of a solute was obtained by a standard procedure, and the glomerular filtration rate (GFR) was estimated by creatinine clearance (C_{cr}). The amount and fraction of Na^+ transported in the proximal tubule and distal nephron (Henle's loop + distal tubule + collecting duct) were calculated according to the lithium clearance method (Thomsen & Schou, 1986). The principle of the method is as follows: The lithium ion (Li^+) is reabsorbed in the proximal tubule to the same extent as water and Na^+, but ordinarily it is not reabsorbed in the loop of Henle, distal tubule and collecting duct, nor is it secreted. Accordingly, the fraction of the filtered Li^+ load that is excreted in the urine is identical to the fraction of filtered water and Na^+ that is delivered from the proximal tubule. The excreted fraction of filtered Li^+ can be determined as the lithium clearance (C_{Li}) divided by GFR. It is, therefore, possible to calculate flows along the tubular system. Because C_{Li} /GFR represents the fractional delivery of water and Na^+ from the proximal tubule, C_{Li} is a measure of the absolute amounts of water and Na^+ that leave the proximal tubules. Expressions for tubular Na^+ handling are as follows:

$$F_{Na} = GFR \times P_{Na}$$
$$DD_{Na} = C_{Li} \times P_{Na}$$
$$APR_{Na} = F_{Na} - DD_{Na}$$
$$ADR_{Na} = DD_{Na} - U_{Na}\ V$$
$$FPR_{Na} = (APR_{Na}/F_{Na}) \times 100\%$$
$$FDR_{Na} = (ADR_{Na}/DD_{Na}) \times 100\%$$

where F_{Na} is filtered Na^+ load, P_{Na} is plasma Na^+ concentration, DD_{Na} is distal Na^+ delivery, C_{Li} is lithium clearance, APR_{Na} is absolute proximal Na^+ reabsorption, ADR_{Na} is absolute distal Na^+ reabsorption, U_{Na} V is urinary Na^+ excretion, FPR_{Na} is fractional proximal Na^+ reabsorption, and FDR_{Na} is fractional distal Na^+ reabsorption.

Statistical analysis

All results were presented as the mean±S.E. Statistical evaluation of the data was done using the Student's *t*-test (unpaired comparison). Differences with $p<0.05$ were considered significant.

RESULTS

General renal functions

Table 1 shows the effects of cadmium treatment on urine flow (V), urine osmolality (U_{osm}) and creatinine clearance (C_{cr}). The V increased markedly after 3 weeks of cadmium treatment, showing a typical polyuria of cadmium intoxication. The average V of cadmium group was 32.9±4.5 ml/kg/day, which was nearly two-fold greater than the corresponding value in the control group (17.5±1.2, $p<0.01$). On the other hand, the urine osmolality (U_{osm}) decreased significantly after 3 weeks of cadmium treatment (hyposthenuria). The average U_{osm} of the cadmium group (1529±120 mOsm/kg H_2O) was only about 65% of the corresponding control value (2351±95, $p<0.01$). The glomerular filtration rate (GFR), estimated by creatinine clearance (C_{cr}), was not altered by 1-week cadmium treatment, but it was significantly reduced after 2 or 3 weeks of cadmium treatment. The C_{cr} of the cadmium group at the end of 3-week treatment (2.23±0.23 ml/kg day) was only about 40% of the control value (5.64±0.29, $p<0.001$).

Renal sodium handling

Fig. 2 shows the effect of cadmium treatment on

Table 1. Urine flow (V), urine osmolality (U_{osm}), and creatine clearance (C_{cr}) in control (Cont.) and cadmium treated (Cd) rats

		Weeks of treatment			
		0	1	2	3
V	Cont.	24.2±1.3	19.2±1.5	18.8±1.8	17.5±1.2
(ml/kg/day)	Cd	24.8±1.2	16.1±1.4	23.7±4.3	32.9±4.5*
U_{osm}	Cont.	1782±122	2093±122	2316±121	2351±95
(mOsm/kg H_2O)	Cd	1620±77	2273±73	2165±123	1529±120*
C_{cr}	Cont.	4.52±0.29	4.84±0.19	5.71±0.20	5.64±0.29
(l/kg/day)	Cd	4.53±0.25	4.35±0.15	3.18±0.26*	2.23±0.20*

Values represent mean±SE of 8~18 rats. *significantly different ($p<0.05$) from the corresponding control value.

Table 2. Fractional Na^+ reabsorption in the proximal tubule and distal nephron of control (Cont.) and cadmium treated (Cd) rats assessed by Li clearance technique

		Weeks of treatment			
		0	1	2	3
FPR_{Na}	Cont.	67.08±2.06	70.76±1.35	74.52±1.78	74.24±1.88
(%)	Cd	62.14±2.97	78.10±2.40*	61.47±6.91	53.06±0.39*
FDR_{Na}	Cont.	98.99±0.13	99.15±0.16	99.15±0.16	99.40±0.06
(%)	Cd	98.93±0.09	99.74±0.05*	99.40±0.12	99.06±0.39

FPR_{Na}: fractional proximal tubular Na^+ reabsorption, FDR_{Na}: fractional distal nephron Na^+ reabsorption. Values represent mean±SE of 8~18 rats. *significantly different ($p<0.05$) from the corresponding control value.

renal Na^+ excretion. In the early phase (first week) of cadmium treatment, the filtered Na^+ load (F_{Na}) was not changed, but the urinary Na^+ excretion (U_{Na} V) was drastically reduced to less than 25% of the control value (0.46±0.13 mEq/kg/day vs. 1.80±0.40 in the control, $p<0.001$). As a consequence, the fractional Na^+ excretion (FE_{Na}) was markedly depressed (0.07±0.02% vs. 0.40±0.04 in the control, $p<0.001$).

Table 2 shows the fractional Na^+ reabsorption in the proximal tubule (FPR_{Na}) and distal nephron (FDR_{Na}) determined by lithium clearance technique. The Na^+ reabsorption was significantly increased in both the proximal tubule (78.10±2.40% vs. 70.76±1.35 in the control, $p<0.05$) and distal nephron (99.74±0.05% vs. 99.15±0.16 in the control, $p<0.001$) after 1-week of cadmium treatment. This indicates that the reduction in urinary Na^+ excretion in the early phase of cadmium treatment was due to increase in Na^+ reabsorption in both the proximal tubule and distal nephron.

During the late phase (third week) of cadmium treatment, the filtered Na^+ load (F_{Na}) was reduced to less than 40% of the control value (306±28 mEq/kg/day vs. 786±40 in the control, $p<0.001$). However, the absolute amount of Na^+ excretion (U_{Na} V) was not significantly different from the control; thus, the fractional Na^+ excretion (FE_{Na}) appeared to be significantly increased (Fig. 2). The lithium clearance data (Table 2) indicated that the fractional Na^+ reabsorption was decreased in the proximal tubule (53.06±0.39% vs. 74.24±1.88 in the control, $p<0.005$), but not in the distal nephron (99.06±0.39% vs. 99.40±0.06 in the control, NS).

Renal potassium handling

As depicted in Fig. 3, during the early phase (first

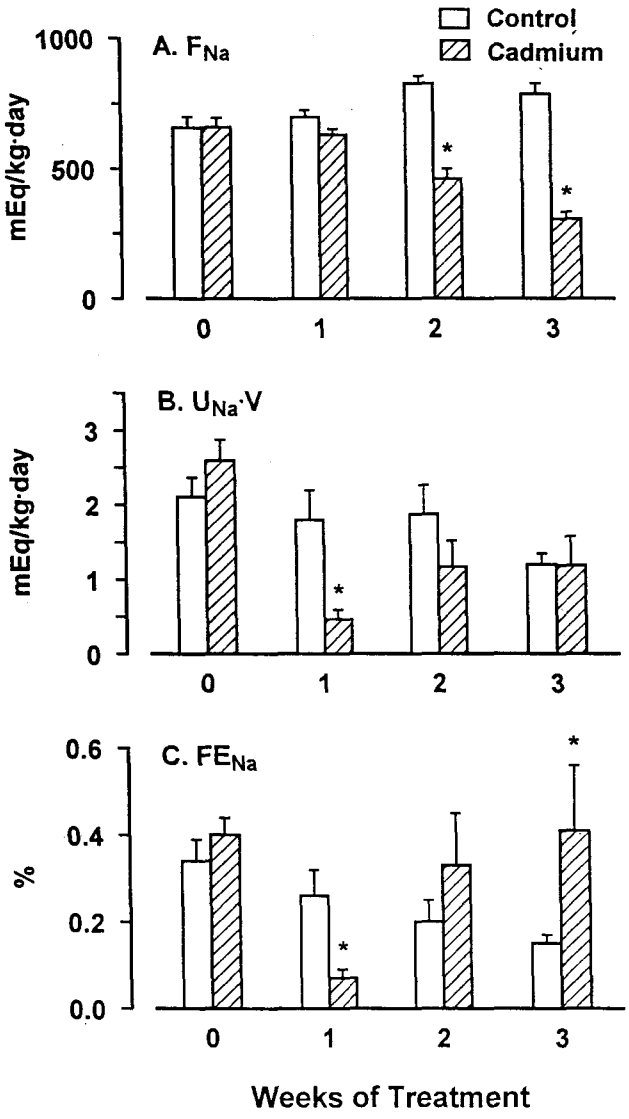

Fig. 2. Effect of cadmium treatment on renal sodium excretion. A: filtered load (F_{Na}), B: absolute amount of urinary excretion (U_{Na} V), C: fractional excretion(FE_{Na}). Values represent the mean+1 S.E. of 8~18 animals. *significantly different from the control group ($p<0.05$).

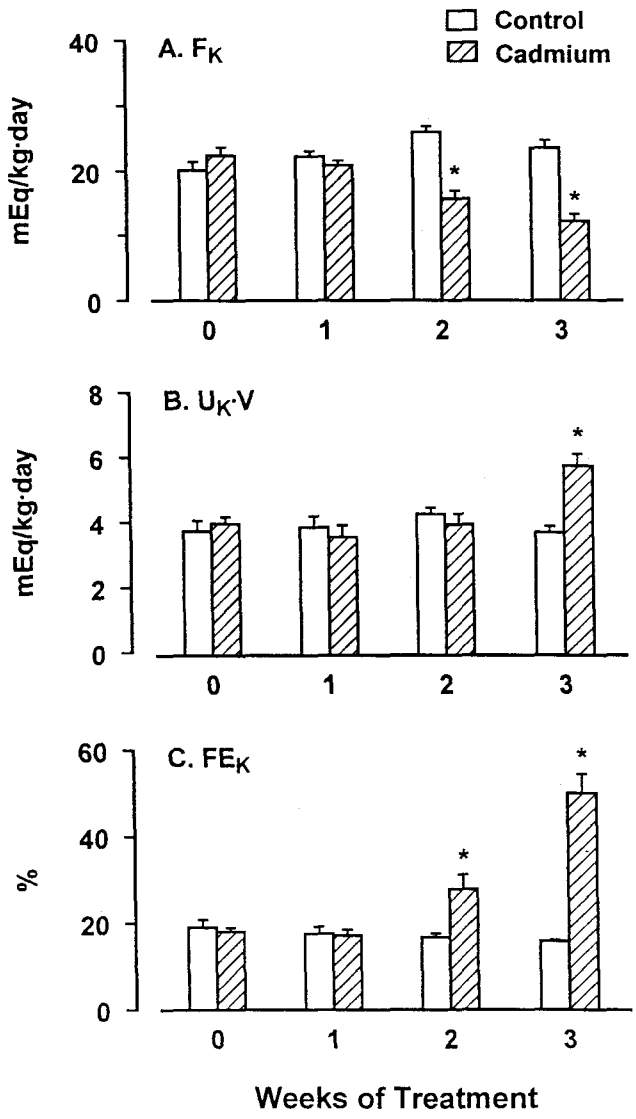

Fig. 3. Effect of cadmium treatment on renal potassium excretion. A: filtered load (F_K), B: absolute amount of urinary excretion (U_K V), C: fractional excretion(FE_K). Values represent the mean+1 S.E. of 8~18 animals. *significantly different from the control group ($p<0.05$).

week) of cadmium treatment, both the filtered load and urinary excretion (both absolute and fractional) of K^+ were not significantly altered. During the later phase (second and third weeks) of cadmium treatment, the filtered load of K^+ was significantly decreased, mainly due to reduced GFR (Table 1). However, the urinary K^+ excretion was significantly elevated, such that the fractional excretion was approximately three-fold greater than that of the control group.

DISCUSSION

Sodium excretion

In the cadmium group, the Na^+ excretion declined drastically during the early phase of cadmium treatment and returned to the control level during the later phase (Fig. 2). Similar findings were observed in previous experiments (Kim et al, 1988: Kim & Park, 1989), however, the underlying mechanisms remain to be elucidated.

The lithium clearance experiment in the present study indicated that the early reduction of Na^+ excretion was due to the activation of Na^+ transport in both the proximal and distal nephrons. The values of fractional Na^+ reabsorption in the proximal tubule and distal nephron were all significantly increased after 1-week of cadmium treatment (Table 2). The mechanism by which proximal tubular Na^+ transport was activated is not completely understood, but it may be attributed, in part, to an increase in Na^+ pump capacity. Previous study (Kim & Park, 1989) have shown that the renal cortical microsomal Na^+-K^+-ATPase activity is significantly increased after 1-week of cadmium treatment. The rise in distal Na^+ reabsorption was most likely attributed to an elevation of aldosterone secretion, as supported by previous study (Kim & Park, 1989). A similar conclusion was made by Nishiyama & Nakamura (1984), who observed a marked increase in plasma aldosterone in rats during 7 days of cadmium treatment (2 mg/kg/day). Regardless of the mechanism, the present study suggests that the Na^+ retention and hypertension observed in short-term cadmium exposed animals (Perry & Ealanger, 1971; Doyle et al, 1975; Schroeder, 1964, 1965; Schroeder & Buckman, 1967, Schroeder et al, 1968) might be due to an increase in Na^+ transport in the proximal and distal renal tubules.

During the late phase (second and third week) of cadmium exposures, return of Na^+ excretion to the control level, despite the reduction in filtered Na^+ load (Fig. 2A and B), implies that the renal tubular Na^+ reabsorption was inhibited. In fact, the value of fractional Na^+ excretion (FE_{Na}) at the end of 3-week treatment appeared to be two-fold greater in the cadmium group compared to the control group (Fig. 2C). Lithium clearance study indicated that the fractional Na^+ reabsorption was reduced in the proximal tubule but not in the distal nephron (Table 2). Thus, the Na^+ transport was inhibited specifically in the proximal tubule. This inhibition of Na^+ transport was probably associated with impairment of Na^+ transport systems in both the luminal and peritubular membranes of proximal tubular cell. Previous studies on renal cortical brush-border membrane vesicles isolated from cadmium-intoxicated rats (Lee et al, 1990, 1991; Kim et al, 1990; Kim & Park, 1995; Ahn & Park, 1995; Park et al, 1997) showed that the Na^+-cotransport systems for glucose, amino acids, dicarboxylate, and inorganic phosphate are all significantly impaired, indicating that the luminal membrane Na^+ transport coupled with other solute transports could be retarded by the cadmium intoxication. The Na^+-K^+-ATPase activity of renal cortical microsomes was significantly attenuated after 3 weeks of cadmium treatment in a previous study (Kim & Park, 1989), suggesting that the Na^+ pump capacity in the basolateral membrane was impaired.

Taken together, the available data indicate that the cadmium exposure has differential effects on the renal tubular Na^+ transport depending on the exposure period. During acute and short-term exposures, the Na^+ transport is activated in most nephron segments, whereas after prolonged exposures, the Na^+ transport is inhibited, especially in the proximal tubule. The latter effect may be associated with gradual accumulation of cadmium exclusively in the proximal tubular cell (Kjellstrom, 1986) by the endocytic process of cadmium-metalothionein complex (Nordberg et al, 1974; Nordberg, 1978).

Potassium excretion

The K^+ excretion did not undergo significant variations during the early phase (first week) of cadmium treatment, but it rose drastically during the later phase (third week) despite a reduction in filtered load (Fig. 3). Such changes in K^+ excretion may be associated with variations in proximal tubular transport of Na^+ and other solutes. It is known that the urinary excretion of K^+ is largely determined by the amount of K^+ secretion in the distal tubule, which, in turn, is altered by Na^+ delivery to the distal tubule, the distal tubular flow rate, and the peritubular K^+ uptake (Giebisch, 1983).

In this study, the proximal tubular fractional Na^+ reabsorption was increased in the early phase of cadmium treatment (Table 2). A consequent reduction of distal Na^+ delivery (137 ± 17 mEq/kg/day vs. 202 ± 8 in the control, $p<0.01$) resulted in a fall in Na^+ reabsorption in the distal nephron (136 ± 17 mEq/kg/day vs. 200 ± 8 in control, $p<0.01$), which would cause a decrease in luminal negative potential, a driving force for K^+ secretion (Giebisch, 1983). On the other hand, an increase in aldosterone secretion at this stage (Kim & Park, 1989) would facilitate distal tubular K^+ secretion by stimulating the peritubular K^+ uptake (Williams & Dluhy, 1972; Katz, 1982). We speculate that these two opposite effects canceled each other, causing the urinary K^+ excretion

to remain unchanged.

In the late phase of cadmium treatment, the fractional reabsorption of Na^+ (and fluid) in the proximal tubule was reduced as judged by lithium clearance technique (Table 2). This would cause a relative increase in Na^+ and fluid deliveries to the distal nephron. In fact, the urine flow (V) of the cadmium group at this stage was 88% higher than that of the control group (Table 1). Under this condition, the driving force for K^+ secretion in the distal tubule could be increased by facilitated wash out of K^+ from the tubular lumen (Giebisch, 1983); consequently, the urinary K^+ excretion could be increased. Another possible mechanism for the rise in urinary K^+ output is the increased excretion of impermeable anions. Previous studies (Adams et al, 1969; Iwao et al, 1980; Kim et al, 1988; Kim & Park, 1989) have shown that the urinary excretion of phosphate is markedly increased by cadmium intoxication. A large amount of anions like phosphate in the distal tubular lumen would facilitate K^+ secretion by changing the electrical potential gradient across the luminal membrane (Giebisch, 1983).

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