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Increased Arterial Potassium Transport in Reduced Renal Mass Hypertension of the Rat (42333)

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Abstract. Aortic potassium turnover was studied during the development of hypertension induced by salt load in male rats after 70–75% of total renal mass was removed. Systolic blood pressure in the saline-drinking experimental reduced renal mass (RRM) rats steadily increased until the fourth week after surgery and thereafter stayed at the same level. Control RRM rats given tap water for drinking, and unilaterally nephrectomized saline-drinking control rats maintained normal blood pressure. Compared to controls, experimental RRM rats exhibited increased plasma aldosterone concentration while plasma renin activity was low in all groups with no significant difference. Aortic hypertrophy, greater ^{42}K turnover, and elevated ^{42}K exchange were observed with experimental RRM hypertension. Sensitivity to the effect of norepinephrine (NE) on aortic ^{42}K turnover was increased four- to ninefold in the experimental RRM group as compared to controls. These results indicate that reduced renal mass hypertension is associated with increased potassium permeability and NE supersensitivity in vascular smooth muscle.

As in the Chanutin–Ferris type of hypertension (1) in which one kidney and the poles of the other kidney were removed, reduction of renal mass when accompanied by a sodium load markedly increases blood pressure (2–5). Suppression of plasma renin activity, hemodynamic changes, and deficiency of renomedullary interstitial cells were associated with elevated blood pressure in those reduced renal mass hypertensive (RRM) rats (3–5). Reduction in renal mass was associated with increased extracellular fluid volume without any significant change in serum sodium concentration or water accumulation in the intravascular space (3, 6). Reduced ouabain-sensitive ion fluxes into arteries were reported in reduced renal mass hypertension (5). The same decreases in ^{86}Rb uptake were also observed with deoxycorticosterone acetate (DOCA)-salt and one-kidney renal hypertension (7, 8), leading to a conclusion that volume-expanded low renin forms of experimental hypertension are accompanied by suppression of the Na^+–K^+ pump activity in vascular tissues possibly by a circulating sodium transport inhibitor (5).

Radioisotopic measures of sodium, potassium, and chloride fluxes have shown increased turnover in vascular smooth muscle from spontaneously hypertensive rats (9, 10), DOCA-salt hypertensive rats (11–13), and aldosterone-induced hypertension (14). Increased ionic turnover also occurs in the vascular smooth muscle during exposure to norepinephrine (NE) and other vasoconstrictor substances (14, 15). Supersensitivity of ion flux changes to NE has also been found in several forms of hypertension (9, 12, 14), and may be an important factor leading to increased peripheral resistance. Considering the association of altered vascular ion metabolism with hypertension of various forms, it was the objective of this study to investigate such relationship in reduced renal mass hypertension. Preliminary results of this study have appeared in an abstract (16).

Materials and Methods. *Animals and tissues.* Male Sprague–Dawley rats weighing 150–180 g, and anesthetized with ether were subjected to partial nephrectomy. The upper and lower poles of the right kidney were removed with a scalpel blade and bleeding was controlled by Gelfoam (Upjohn Co., Kalamazoo, Mich.). The surgical procedure reduced 40 to 50% of the right kidney mass leaving a renal segment containing papilla, outer medulla, and cortex immediately lateral to these two compartments. A group of rats (one kidney) was sham-operated. Following the

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partial nephrectomy and sham-operation, animals were fed normal rat chow containing 0.14 meq Na and 0.28 meq K per g and tap water for 1 week. The left kidney was then removed from both reduced renal mass (RRM) and one-kidney groups. The RRM rats were divided into two groups: The experimental group of RRM rats received 1% saline and the control group of RRM rats was given tap water as drinking fluid. One-kidney control animals also received 1% saline. All animals were fed with normal rat chow *ad libitum* during the experimental period of 7 weeks. There were two groups of rats (RRM–tap water and one-kidney-saline) in this study to serve as controls because subtotal nephrectomy has been reported to produce uremia, which in itself could have several secondary effects (17, 18), and comparisons of experimental data of uremic rats to those from nonuremic rats may lead to erroneous conclusions. Body weight and systolic blood pressure (by a tail-cuff method) were determined twice per week. During the fifth week after surgery, fluid intake and 24-hr urine volume were determined on rats which were housed for 5 days in metabolism cages. During the seventh week the rats were decapitated by a guillotine and were bled into chilled polyethylene tubes containing disodium ethylenediaminetetraacetate (EDTA). Plasma samples were separated by centrifugation and kept frozen at −60°C for assay of aldosterone and renin activity. The thoracic aorta was immediately removed and placed in a K-free dissection solution containing 0.25 m*M* Ca^{2+} at room temperature. The tissue was dissected free of fat and loose connective tissue and remained in this solution for 1 to 1.5 hr in order to deplete endogenous K contents. This procedure insured nearly 100% exchange with ^{42}K during isotope loading (11). The vessels were slit lengthwise, the length measured, and they were then mounted on stainless-steel holders. The wet weight of the tissue was determined at the end of the experiment to obtain a weight-to-length ratio. The kidney was also removed and weighed.

Solutions. The normal physiological solution contained the following components in millimolar: Na^+, 146.2; K^+, 5.0; Mg^{2+}, 1.2; Ca^{2+}, 2.5; Cl^-, 143.9; HCO_3^-, 13.5; $H_2PO_4^-$, 1.2; and glucose, 11.4. Solutions were bubbled with a 97% O_2–3% CO_2 mixture at 37°C resulting in a pH of 7.4. Norepinephrine (Winthrop) solutions for the concentration–response experiments were prepared by serial dilution with normal physiological medium to which 0.025 m*M* EDTA was added to delay oxidation of the drug.

Isotope techniques. These procedures have been previously described in detail (9–11). Aortas were equilibrated at 37°C in normal physiological salt solution containing ^{42}K (University of Missouri Research Reactor) for 3 hr. After a 1- to 2-sec rinse, the strips were passed through a series of tubes containing nonradioactive solution. The activity in the tubes and the aorta was counted by a liquid scintillation counter. Washout curves were calculated by sequentially adding the tissue and tube counts in reverse order and then normalizing the counts in terms of percentage initial activity. A digital computer was used to process the data for the isotope washout experiment and to compute the rate, k, at which the counts were washed out into each tube (9). Turnover represents the fraction of the isotope washed out per minute (min^{-1}). The steady-state turnover was the average of the rates measured between 20 and 40 min washout before exposure to NE. The amount of K characterized by slow turnover was derived from the isotope (counts/sec kg^{-1}) remaining in the tissue after a 1-min washout and the specific activity (nmoles/counts sec^{-1}) of the isotope solution (11). The ^{42}K exchange was calculated from the product of the slowly exchanging K and the turnover, k.

The effect of NE on aortic ^{42}K turnover was evaluated in a series of concentration–response experiments. To derive the concentration–response relation, the response to a given concentration of NE (Δk) was calculated as the difference between the highest rate constant obtained during the 10-min exposure to the drug and the rate constant for the washout period just prior to drug exposure. This value was then normalized in terms of Δk_{max}, the response achieved during exposure to a supramaximal concentration of NE (6×10^{-6} *M*). The concentration required to produce a 50% maximal rise in ^{42}K turnover, EC_{50}, was determined for each tissue by interpolation.

Chemical assays. Plasma aldosterone concentration and renin activity were determined by standard radioimmunoassays (19, 20). The

sodium and potassium concentrations in urine and incubation media were measured by flame photometry.

Statistics. Statistical evaluation of data was performed using the analysis of variance technique and treatment means were compared by the least significance difference (21).

Results. *Development of hypertension.* All experimental and control RRM rats and saline-drinking one-kidney control rats appeared healthy throughout the study. Systolic blood pressure in the saline-drinking experimental RRM rats steadily increased to hypertensive levels by the fourth week after subtotal nephrectomy and thereafter remained at the same level. The blood pressure in tap-water-drinking RRM control and saline-drinking one-kidney control rats remained at normotensive levels during the experimental period. The final blood pressure in the experimental RRM rats was significantly ($P < 0.01$) higher than tap-water-drinking RRM or saline-drinking one-kidney control rats (Table 1). Tap-water-drinking RRM and one-kidney control rats had greater body weights than the experimental RRM group (Table 1). On the other hand, aortic hypertrophy was observed in experimental RRM rats. The plasma aldosterone concentration was greater in the experimental RRM group as compared to control groups. The plasma renin activity was suppressed in all rats as compared to the value in intact rats with normal Na (22), and no difference was observed between groups. The fluid intake of the experimental RRM group was about doubled, compared to that of one-kidney control rats and tripled as compared to that in the control RRM group. Subsequently, urine volume and urinary Na excretion were significantly greater in the experimental RRM group. Urinary potassium excretion was less in the experimental RRM group as compared to control groups.

Potassium turnover. A significant increase in the steady-state ^{42}K turnover occurred in aortas from experimental RRM rats as compared to both control groups of rats (Table 2). Slowly exchanging ^{42}K content was also greater in the experimental RRM group as compared with both control groups of rats: The potassium exchange was about doubled in the experimental RRM group.

Norepinephrine responses. Exposure to NE resulted in concentration-dependent increases in ^{42}K turnover as shown in Fig. 1. The maximal changes in the rate of ^{42}K turnover (NE, 5×10^{-6} *M*) was greater ($P < 0.01$) in control RRM rats (0.024 ± 0.001 min^{-1}) as compared to the experimental RRM (0.018 ± 0.001 min^{-1}) or one-kidney control (0.018 ± 0.002 min^{-1}) group. The concentration–response curve was shifted to the left (Fig. 2) and the EC_{50} of NE was significantly ($P < 0.01$) less in experimental RRM rats ($0.32 \pm 0.07 \times 10^{-8}$ *M*) than the value of the one-kidney control group ($1.32 \pm 0.26 \times 10^{-8}$ *M*) or control RRM rats ($2.75 \pm 0.45 \times 10^{-8}$ *M*). These findings indicate an increased sensitivity in the aorta

TABLE I. ANALYSES OF TISSUES AND FLUIDS FROM CONTROL AND EXPERIMENTAL RATS[a]

	One kidney	Reduced renal mass		*P* value	
	Saline (A)	Tap water (B)	Saline (C)	A vs C	B vs C
No. of rats	5	5	6		
Body weight (g)	317 ± 18	338 ± 9	242 ± 8	0.01	0.001
Final blood pressure (mm Hg)	115 ± 7	119 ± 5	176 ± 8	0.001	0.001
Kidney weight (g)	1.92 ± 0.16	1.61 ± 0.08	1.66 ± 0.07	NS[b]	NS
Aortic weight per length (mg/cm)	11.27 ± 0.31	—	12.67 ± 0.37	0.05	—
Plasma aldosterone (ng/100 ml)	10.3 ± 2.5	11.2 ± 1.8	18.9 ± 1.4	0.01	0.05
Plasma renin activity (ng AI/ml/hr)	0.47 ± 0.16	0.25 ± 0.16	0.27 ± 0.14	NS	NS
Fluid consumption (ml/24 hr)	67 ± 10	45 ± 5	132 ± 13	0.01	0.001
Urine volume (ml/24 hr)	41 ± 4	28 ± 4	103 ± 17	0.01	0.001
Urinary Na (meq/24 hr)	13.2 ± 0.9	3.4 ± 0.2	22.9 ± 3.2	0.01	0.001
Urinary K (meq/24 hr)	5.0 ± 0.2	5.1 ± 0.3	3.4 ± 0.4	0.01	0.01

[a] All values are means ± SEM.
[b] NS: Not significantly different ($P > 0.05$).

TABLE II. POTASSIUM TURNOVER IN AORTAS FROM CONTROL AND EXPERIMENTAL RATS[a]

	One kidney	Reduced renal mass		*P* value	
	Saline (A)	Tap water (B)	Saline (C)	A vs C	B vs C
No. of rats	5	5	6		
^{42}K turnover (min^{-1})	0.0091 ± 0.0005	0.0101 ± 0.0004	0.0162 ± 0.0007	0.001	0.001
Slow ^{42}K (mmole/kg wet wt)	32.7 ± 0.6	39.2 ± 0.9	45.6 ± 1.0	0.001	0.01
^{42}K exchange (mmole/kg wet wt min^{-1})	0.298 ± 0.007	0.398 ± 0.014	0.738 ± 0.026	0.001	0.001

[a] All values are means ± SEM.

to NE developed in saline-drinking hypertensive RRM rats.

Discussion. The results of the present study indicate that high sodium intake (drinking saline) induces hypertension in RRM rats, whereas normal sodium intake (drinking tap water) did not. Several investigators (23–26) observed a mild hypertension in RRM rats when fed with a normal sodium diet and given tap water as drinking fluid. The surgical procedures used to reduce the renal mass in the present study were slightly different from those used in previous studies and the degree of tissue damages caused by the surgical procedures between the present study and previous studies (23–26) might be different. A small difference in functional renal mass in RRM rats is critical to maintain the blood pressure. Consequently, RRM rats in the present study appeared to be able to maintain normal sodium metabolism and blood pressure with normal sodium intake. The one-kidney control rats given saline for drinking also remained normotensive throughout the experimental period. The magnitude of increases in blood pressure was similar to those reported previously for the experimental RRM rats (3–5). In RRM dogs, which received saline as a drinking fluid, the steady level of high blood pressure was achieved much earlier (2, 6). The increases in fluid intake and urinary sodium excretion in experimental RRM rats, which were nearly twice the control groups, agree with the previous findings (3, 4). The reason for the decrease in urinary potassium excretion in experimental RRM rats is not clear. The higher

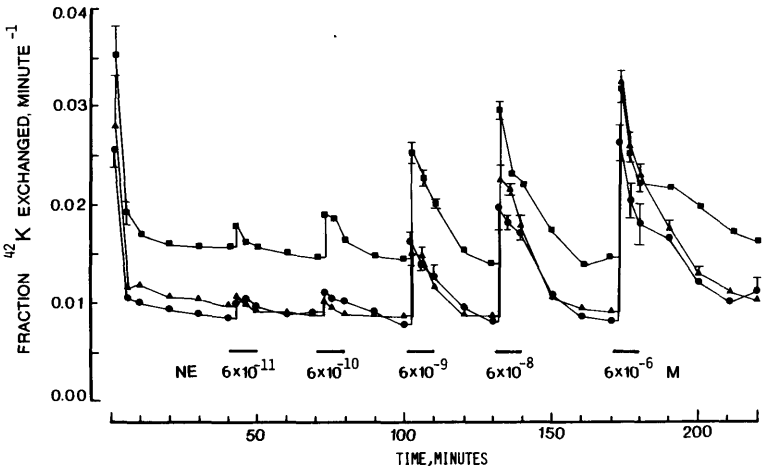

FIG. 1. Effects of NE on the rate of ^{42}K washout in aorta from six experimental reduced renal mass (RRM)-saline (■), five RRM-tap-water control (▲), and five one-kidney-saline control (●) rats. The horizontal bars indicate the time of exposure to NE at the indicated concentration. Vertical bars indicate ±SEM.

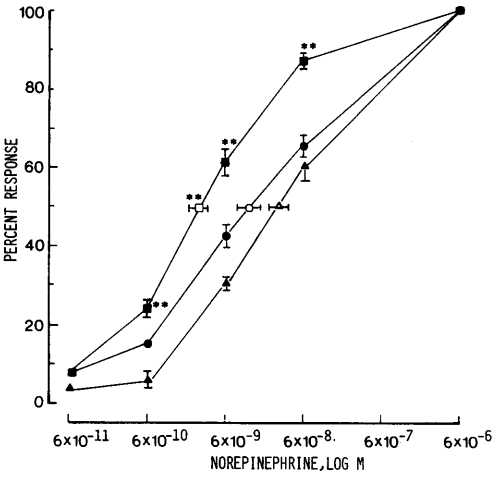

FIG. 2. Concentration–response relations in six experimental reduced renal mass (RRM)-saline (■), five RRM-tap-water control (▲), and five one-kidney-saline control (●) rats. The EC_{50} are indicated by open symbols. Vertical and horizontal bars indicate ±SEM. Experimental RRM-saline animals were significantly different (**$P < 0.01$) from RRM-tap-water or one-kidney-saline control groups.

intake of sodium in experimental RRM rats might have promoted kaliuresis during the early period of hypertensive development (17) and possibly decreased total body potassium due to negative potassium balance. Such a reduction might contribute to the decreased potassium excretion during the chronic stage.

Both the reduction in renal mass and chronic salt loading would be expected to decrease plasma renin levels (23, 27). Ylitalo *et al.* (23) reported that the renin activity in RRM rats was decreased by increasing the sodium intake. The reduction in renal mass in the same experiment also showed lower renin activity as compared with sham-operated control rats. However, in the present study, the plasma renin activity in tap-water-drinking RRM rats was suppressed almost to the nondetectable level and no further reduction in the plasma renin activity was observed with increased sodium intake in experimental RRM rats. Many factors, including the renin–angiotensin system, can influence plasma aldosterone levels (27, 28). The increased plasma aldosterone concentration in the saline-drinking experimental RRM rats as compared to tap-water-drinking RRM controls is just opposite to the expectation, and the explanation for that increase is not presently available. The elevated plasma aldosterone levels in the experimental RRM animals is hardly attributable to the secondary effect of uremia since the aldosterone level in the control RRM rats was within the normal range (28).

Haddy and associates (5, 8) have suggested that decreased Na^+–K^+ pump activity in vascular tissues results from a Na^+ transport inhibitor and that this decrease represents a major pathogenic mechanism for the development of RRM hypertension. The morphologic and functional alterations of the renomedullary interstitial cells in the remaining renal segment after subtotal nephrectomy surgery in RRM rats have also been proposed to be a mechanism which contributes to RRM hypertension (4). This proposal was supported by a demonstration that transplanted normotensive renomedullary interstitial cells are antihypertensive while those renomedullary interstitial cells transplanted from RRM rats did not convey antihypertensive effects. However, the pathogenic mechanism responsible for the development of hypertension in sodium-loaded RRM rats has not been clearly defined.

The steady-state isotope efflux studies provide a basis for computing the passive membrane permeability (29). Because both monovalent anions and cations are involved in the hypertensive changes, it was suggested that a significant elevation in membrane permeability was associated with spontaneously hypertensive rats (9), DOCA (11), and aldosterone-induced hypertension (14). The significant increases of ^{42}K turnover in experimental hypertensive RRM rats indicate that membrane permeability may be increased as compared with that of control RRM rats or one-kidney controls, and that the magnitude of the change in experimental RRM rats is comparable to mineralocorticoid-salt hypertensive rats (11, 14).

Several links between membrane permeability and vessel wall tension such as membrane potential, and calcium influx and release have been reported (10). The increased ^{42}K turnover and increased effect of NE on ^{42}K turnover provide an ionic basis for increased contractile activity. It has been suggested that increased permeability of the membrane to K^+ would be associated with partial membrane

cluding arrest of the energy producing oxidative metabolism during the various cold storage periods (5–7).

We cannot exclude the possibility of a delayed effect of trace amounts of trypan blue taken up by visually unstained fetal islets. Trypan blue has been recognized as a mutagen as well as a carcinogen (8, 9) in experimental animals, but recent studies have indicated that up to 1 year of chronic protracted exposure to trypan blue was required to induce, e.g., reticuloendothelial neoplasm, predominantly in the liver and lymphomas (10, 11). Therefore, we expect that 15 min *in vitro* exposure of the human fetal islets to trypan blue would have negligible physiological effects on viable functional fetal islets and would not place the recipient of tissue treated in this manner at risk.

Our data, therefore, suggest that the *in vitro* trypan blue staining technique, in comparison to the time consuming assay of fractional stimulated insulin secretion rates, provides a rapid nondestructive means of analysis of the viability of human fetal islets for transplantation and may be used as a satisfactory way of assessing their potential in providing a functional graft.

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