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Research Paper

Interaction of sodium loading and enalapril on renin mRNA and renin release in hydronephrotic mice

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Abstract: The present study investigated the interaction between sodium loading and enalapril on renin synthesis and secretion in hydronephrotic mice. Four different experimental groups (n=10 each) were used: sham-operated animals with normal diet (control group); sodium loading (SL group); enalapril treatment with normal diet (E group), and sodium loading combined with enalapril treatment (SL+E group). The hydronephrotic left kidney was induced by unilateral ureteral ligation in mice in the latter three groups. Plasma renin concentration (PRC) in the aorta, both the left and right renal veins, tissue renin concentration (TRC) and renin mRNA levels in the kidneys were examined under different procedures. In hydronephrotic mice treated with sodium loading, PRC in the left and right renal veins was lower than that in control mice (P<0.05), and TRC and renin mRNA levels in the hydronephrotic kidney were also suppressed (P<0.05). In hydronephrotic mice treated with enalapril, there were significant increases in PRC, TRC and renin mRNA levels in the hydronephrotic and right kidneys compared to the normal control (P<0.01). In hydronephrotic animals treated with sodium loading and enalapril, the increasing response was attenuated, and PRC in the hydronephrotic vein was similar to the level in the aorta. There was an interaction between sodium loading and enalapril on renin-angiotensin system (RAS) in both hydronephrotic and normal kidneys. The mechanism in control of renin synthesis is independent of the macula densa, but the latter is critical in the control of renin secretion.

Key words: renin synthesis; sodium loading; hydronephrosis; macula densa; enalapril; ureter

钠负荷及依那普利对肾积水小鼠肾素合成与分泌的相互作用

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摘 要：本文应用肾积水小鼠，探讨了钠负荷及依那普利(enalapril)对肾素合成及分泌的相互作用。实验动物分为 4 组：假手术组、钠负荷组、依那普利组、钠负荷及依那普利联合组。Balb/C 小鼠采用左侧输尿管结扎形成肾积水。在不同的条件下，对主动脉及双侧肾静脉的血浆肾素浓度(plasma renin concentration, PRC)、肾组织肾素浓度(tissue renin concentration, TRC)及肾素 mRNA 水平进行了测定。与假手术组相比，钠负荷小鼠中，双侧肾静脉 PRC 降低(P<0.05)，肾积水一侧的 TRC 及肾素 mRNA 也显著降低(P<0.05)。用依那普利治疗肾积水小鼠后，PRC、双侧 TRC 及肾素 mRNA 水平高于假手术组(P<0.01)。应用钠负荷及依那普利联合治疗，其效应较单独应用依那普利时为低，肾积水一侧肾静脉 PRC 与主动脉内 PRC 相似。以上结果提示，在正常及肾积水肾脏，钠负荷与依那普利通过相互作用而影响肾素 - 血管紧张素系统(renin-angiotensin system, RAS)。肾素合成的调节可独立于致密斑，但后者对肾素分泌起重要调节作用。

关键词：肾素合成；钠负荷；肾积水；致密斑；依那普利；输尿管
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Renin release is regulated by a number of factors, such as circulating angiotensin II (Ang II)[1-4]. The renin-angiotensin system (RAS) may modify renal function in several ways, i.e. by modulating renal perfusion, glomerular filtration rate (GFR) and tubular sodium reabsorption[3-5]. Circulating Ang II itself exerts a negative feedback on renin release from

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the juxtaglomerular apparatus[6]. The effects of endogenously formed Ang II in the regulation of renin secretion has been examined by pharmacological interruption of the formation of Ang II with angiotensin converting enzyme (ACE) inhibitors, such as captopril or enalapril[7].

Lowering Ang II levels by ACE inhibitor administration leads to decreased circulating aldosterone and natriuresis, and negative sodium balance which may be in part due to the suppression of aldosterone[8,9]. Furthermore, these factors are involved in the response of renin secretion to ACE inhibitor administration. To reduce some of the factors that influence the response to ACE inhibitors, the present study used a mouse model in which one kidney was hydronephrotic thereby removing the effect of the macula densa.

The control of renin secretion has been well documented. It was demonstrated that the negative feedback control of renin is abnormal in hypertensives, because they could not cope with a salt load normally[10,11]. They also showed that treatment with an ACE inhibitor rapidly restored the capacity of the kidney to handle a salt load and normalized blood pressure. However, the effects of ACE inhibitors have never been compared with sodium loading on the activity of the RAS in hydronephrotic animals. Furthermore, the mechanism of their interaction on renin secretion and synthesis remains unclear. Therefore, the aim of the present study was to investigate the mechanism controlling renin synthesis and secretion after the treatment with ACE inhibitor as well as sodium loading by measuring plasma renin, renal renin and renin mRNA levels in both the normal and hydronephrotic kidneys.

1 MATERIALS AND METHODS

1.1 *Animals and experimental procedures*

Male Balb/C mice weighing 25-30 g were used in this study. The animals had free access to normal diet and tap water. The mice were anesthetized by an intraperitoneal injection of 60 mg/kg sodium pentobartitone. In hydronephrotic mice (n=30), the left kidney was exposed by a flank incision and the ureter was doubly ligated with 1.0 silk suture. Antibiotic powder (Cicatrin) was dusted in the abdominal cavity, and the incision was closed. The sham-operated animals (control, n=10) were subjected to the same anesthesia, incision and closure, but without ureter ligation. The total surgery time was 10-15 min per animal. The mice were maintained on a standard laboratory diet and free access to tap water. Six weeks after the operation the left kidney which had its ureter tied was hydronephrotic. At this time the following studies were performed in the animals.

Control group (n=10): The sham-operated mice were given a normal diet and tap water. Sodium loading group (SL group, n=10): The mice with left hydronephrosis were maintained on a normal diet and given 9-fludrocortisone 300 μg/kg per day in 0.5% NaCl drinking water. Enalapril group (E group, n=10): The animals with left hydronephrosis were given enalapril 12 mg/kg per day in their drinking water. SL+E group (n=10): In mice with left hydronephrosis, sodium loading was produced as in SL group, and enalapril was given as in E group.

Seven days after the procedures the mice were sacrificed. A blood sample was taken from the right and left renal veins and the aorta using a puncture, respectively, for the measurement of plasma renin concentration (PRC). The right and left kidneys were removed and used for determining tissue renin concentration (TRC) and renin mRNA level.

1.2 *Measurements of PRC and TRC*

PRC was measured in blood from the aorta and both renal veins using a radioimmunoassay described previously[12]. The value was expressed in mili-Goldblatt Units (mGU) per milliliter of plasma. The kidneys removed from each mouse were weighed and homogenized in 3 mL buffer. Twenty microliter aliquots were used for TRC measurement and TRC was expressed in GU per gram of kidney weight.

1.3 *Measurement of renin mRNA level*

For measurement of renin mRNA level, total RNA in the kidney was extracted using TRIzol reagent (Invitrogen, USA). The amount of RNA extracted was measured by absorbance at 260 nm. An aliquot of each sample of RNA was diluted in 20× standard saline citrate (SSC, 3 mol/L NaCl, 0.3 mol/L sodium citrate) and denatured in formaldehyde. Dilutions of the RNA extract were dotted onto 4 mm diameter spots on pre-wetted nitrocellulose sheets which were then vacuum baked at 80 ºC for 2 h. The filter was then prehybridized at 42 ºC in 10 mL buffer. A 30-mer oligonucleotide probe for mouse kidney renin was labeled at the 5' end with [γ-^{32}P] ATP using T4 polynucleotide kinase (Promega, WI, USA). The labeled probe was then added to hybridization buffer with 15% formamide, and hybridization was allowed to occur overnight at 42 ºC. The filters were washed in the buffer and autoradiographed with hyper-MP film at -70 ºC. The strength of signals on the autoradiograph was measured by a laser densitometer (Molecular Dynamics, CA, USA). To analyze the changes of renin mRNA levels in the kidneys, the results from the

renin signal were expressed relative to that in the control kidney, which was defined as the value of 100 units. The amounts in the other experimental kidneys were expressed as the percentages of control value. The mRNA level was then normalized by the renal tissue weight, as described previously[12].

1.4 *Statistic analysis*

The data are presented as the mean±SEM. The differences in PRC, TRC and renin mRNA levels among the groups were statistically analyzed by one-way ANOVA followed by *post hoc* tests. Paired *t*-test was performed to evaluate the differences in TRC and renin mRNA levels within the same group. The correlations between PRC and TRC, or renin mRNA level were analyzed with PEMS 3.1 for Windows. $P<0.05$ was considered to be statistically significant.

2 RESULTS

All of the animals were in good condition, and at the end of experiments there were no differences in body weights between hydronephrotic and control animals. After unilateral ureteral ligation (UUL), the arterial blood pressure did not differ among the groups. In one week of the experimental procedures, sodium loading did not affect arterial blood pressure. However, enalapril lowered blood pressure in E group. The maximum reduction in blood pressure with enalapril occurred at day 5, from 91 mmHg of the control level to 86 mmHg ($P<0.05$, Fig. 1). In mice treated with sodium loading and enalapril together, blood pressure did not change compared with that in the control group.

2.1 Changes in kidney weight

At the end of the experiment, kidneys in each mouse were removed and weighed. The left kidney weight was (0.29±0.01) g and the right kidney (0.28±0.01) g in control mice. In hydronephrotic mice treated with sodium loading, the left kidney weight [(0.12±0.01) g] was significantly lower than that of the contralateral kidney [(0.28±0.01) g, $P<0.01$]. Similarly, in hydronephrotic mice treated with enalapril, the left hydronephrotic kidney weight was (0.14±0.02) g, less than the right one [(0.29±0.03) g] ($P<0.01$). In hydronephrotic mice treated with sodium loading and enalapril together, the left kidney was (0.12±0.02) g in weight, and lighter than the right kidney [(0.29±0.02) g, $P<0.01$)]. In all mice with left ureteral ligation, urine was contained in the left kidney and produced pressure to the renal tissue, resulting in tubules squeezed and damaged. Light microscopy observation confirmed that the tissue in hydronephrotic kidney was much thinner than that in the control kidney (Fig. 2), leading to the reduction of the tissue weight by removing liquid contained in the kidney at

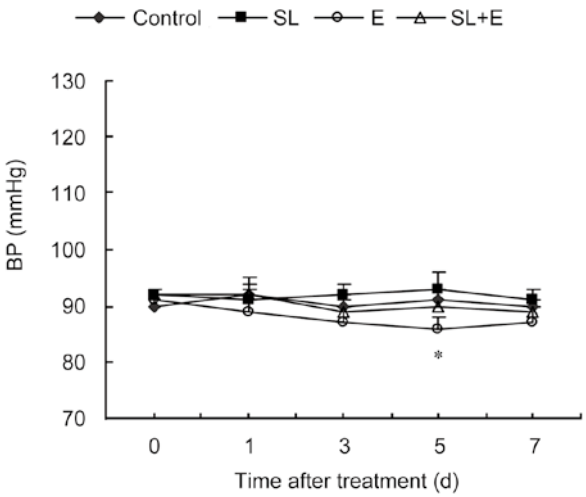

Fig. 1. Effects of sodium loading (SL), enalapril (E) and sodium loading+enalapril (SL+E) on arterial blood pressure (BP). Data are mean±SEM. $n=10$. $^*P<0.05$ *vs* control.

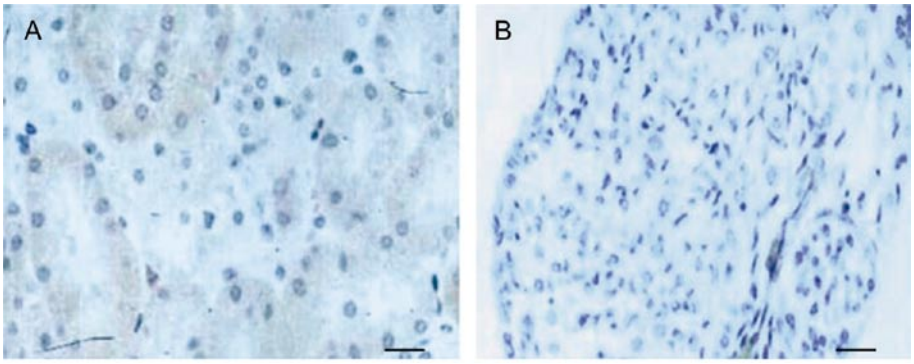

Fig. 2. Serial 3 μm paraffin sections of normal (*A*) and hydronephrotic (*B*) kidneys. In normal kidney the tubules were intact (*A*) while they were disappeared in the hydronephrotic kidney (*B*). Scale bar, 25 μm.

the postmortem.

2.2 Effects of different treatments on PRC

To assess the effects of different procedures on renin release from the kidney, we determined renin concentrations in blood samples taken in random order from the right and left renal veins and aorta. The value from the aorta represents the basal level of renin concentration in the circulation while values from the left and right renal veins refer to the levels of renin secretion from the left and right kidneys, respectively[12]. Changes in PRC caused by sodium loading, enalapril, or sodium loading and enalapril together are shown in Fig. 3.

In control mice, PRC was (19±3) mGU/mL, (34±4) mGU/mL and (32±3) mGU/mL in the aorta, the left and right renal veins, respectively. There was no difference in the value from both the left and right renal veins. The effect of sodium loading on renin secretion was examined in mice in SL group. After seven days of SL treatment, PRC in the aorta decreased to (10±2) mGU/mL, PRC in the right renal vein decreased to (19±1) mGU/mL (P<0.05), and the value from the hydronephrotic vein decreased to (10±2) mGU/mL (P<0.05) compared to the levels in control mice.

After the administration of enalapril in E group, PRC in the aorta increased to (123±15) mGU/mL, elevating 5.5-fold compared to the control level (P<0.01). The value from the right renal vein was (211±20) mGU/mL which was significantly higher (5.2-fold, P<0.01) than that in the control mice. PRC from the left renal vein was (145±18) mGU/mL, lower than that from the right renal vein (P<0.01), but no difference from that in the aorta. These results indicated that enalapril stimulated renin secretion mainly from the normal kidney.

In mice treated with sodium loading and enalapril together (SL+E group), PRC was (58±7) mGU/mL in the aorta and (79±5) mGU/mL in the right renal vein (P<0.05). However, PRC from the left renal vein was (59±5) mGU/mL which did not differ from that in the aorta.

2.3 Effects of different treatments on TRC

The effects of sodium loading, enalapril and both procedures together on TRC in the kidney were examined (see Fig. 4). In control animals, TRC was (54±5) GU/g in the left kidney and (52±4) GU/g in the right kidney. In animals treated with sodium loading for seven days, TRC was (36±3) GU/g in the hydronephrotic kidney and (43±4) GU/g in the right kidney. There was a significant decrease in TRC in the left kidney compared to the control group (P< 0.05).

In mice received enalapril, TRC was (256±38) GU/g (3.7-fold, P<0.01 *vs* control) in the hydronephrotic kidney and (196±11) GU/g (2.7-fold, P<0.01 *vs* control) in the contralateral kidney. There was a significant increase of TRC caused by enalapril in both kidneys, indicating that ACE inhibitor is a potent factor stimulating renin synthesis

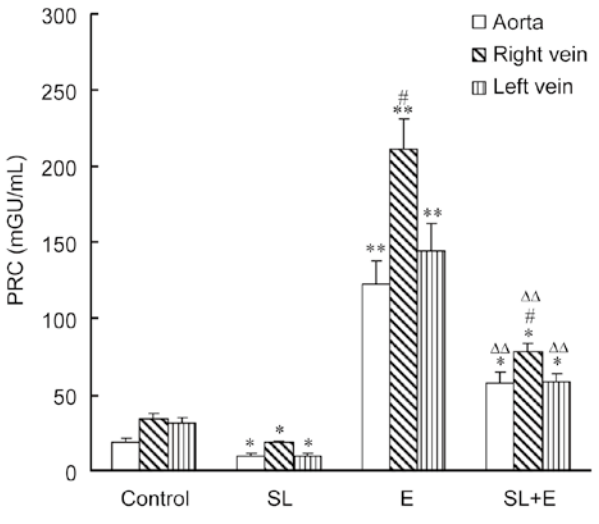

Fig. 3. Changes of PRC in the aorta, right and left renal veins in 4 groups. PRC in blood from the aorta, right and left renal veins in hydronephrotic mice treated with different procedures in the following groups: control, sodium loading (SL), enalapril (E) and sodium loading+enalapril (SL+E). Values are expressed as mean±SEM. n=10. $^{*}P$<0.05, $^{**}P$<0.01 *vs* control; $^{\#}P$<0.05 *vs* aortic value within the same group; $^{\Delta\Delta}P$<0.01 *vs* E group. There was no significant difference between the aorta and left renal vein within the same group.

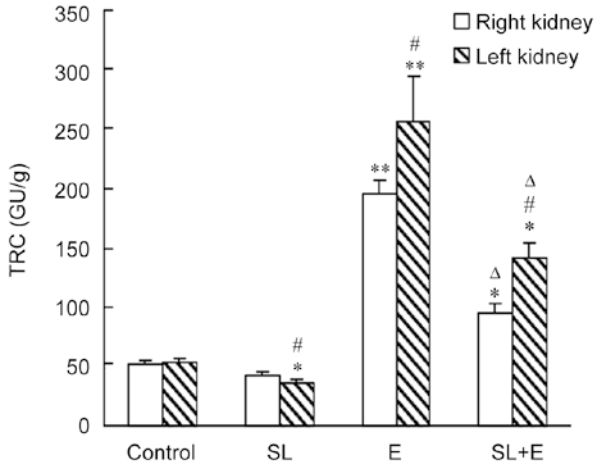

Fig. 4. Changes of TRC in the right and left hydronephrotic kidneys. Mice were treated with different procedures in the following groups: control, sodium loading (SL), enalapril (E) and sodium loading+enalapril (SL+E). Values are mean±SEM. n=10. $^{*}P$<0.05, $^{**}P$<0.01 *vs* control; $^{\#}P$<0.05 *vs* the contralateral value within the same group; $^{\Delta}P$<0.05 *vs* E group.

even during hydronephrosis.

In mice treated with enalapril and sodium loading together, TRC was (142±12) GU/g in the hydronephrotic kidney and (95±8) GU/g in the right kidney (P<0.05). An increase in TRC was seen but the response was attenuated by sodium loading compared to the level in mice with enalapril administration alone (P<0.05). The data clearly showed that there was an interaction between high sodium intake and ACE inhibitor on TRC in the kidney.

2.4 Effects of different treatments on renin mRNA

To study the effects of the experimental procedures on renin gene expression, mice were treated with sodium loading, enalapril or sodium loading in combination with enalapril. Figure 5 shows the changes in renin mRNA levels in kidneys in mice 7 d after treatments. In control mice the level of renin mRNA was 100 units/g in both the left and the right kidneys. In mice with sodium loading, the level of renin mRNA was (73±6)% in the hydronephrotic kidney and (62±8)% in the contralateral kidney (P<0.05). There was a significant decrease in renin mRNA in both kidneys.

In mice treated with enalapril alone, the renin mRNA level was (215±12)% in the right and (175±5)% in the hydronephrotic kidneys (P<0.01). In mice treated with enalapril and sodium loading together, renin mRNA level was (173±7)% in the hydronephrotic kidney and (124±6)% in the right kidney. In SL+E group, renin mRNA was significantly increased in both hydronephrotic and contralateral kidneys compared to control mice, but the response in the contralateral kidney decreased compared to that in E group (P<0.05). A typical autoradiograph of dot-blot for measuring renin mRNA in kidneys is also shown in Fig. 6.

There were positive correlations between PRC and renin

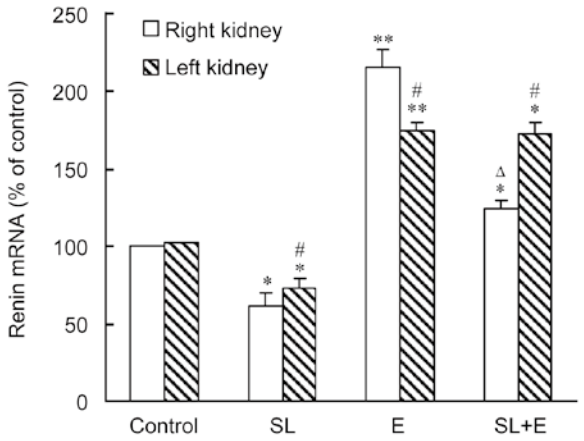

Fig. 5. Changes in renin mRNA levels in both kidneys. Renin mRNA expressed as a percentage of the value in the normal kidney in control mice. Animals were treated with as in the following groups: control, sodium loading (SL), enalapril (E) and sodium loading+enalapril (SL+E). All mice had a left hydronephrotic kidney except control group. Values are mean±SEM. n=10. $^{*}P$<0.05 and $^{**}P$<0.01 *vs* control animals; $^{\#}P$<0.05 *vs* contralateral kidney value within the same group; $^{\Delta}P$<0.05 *vs* E group.

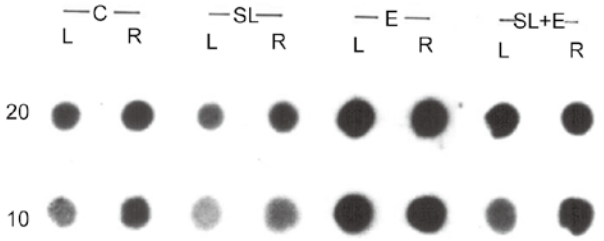

Fig. 6. Renin mRNA in both kidneys from 4 groups of mice. A typical autoradiograph of dot-blot hybridization of renin probe to total RNA from left (L) and right (R) kidneys in mice from the following groups: Control (C); sodium loading (SL); enalapril (E) and sodium loading plus enalapril (SL+E). Amount of total RNA applied, in microgram, is indicated at left.

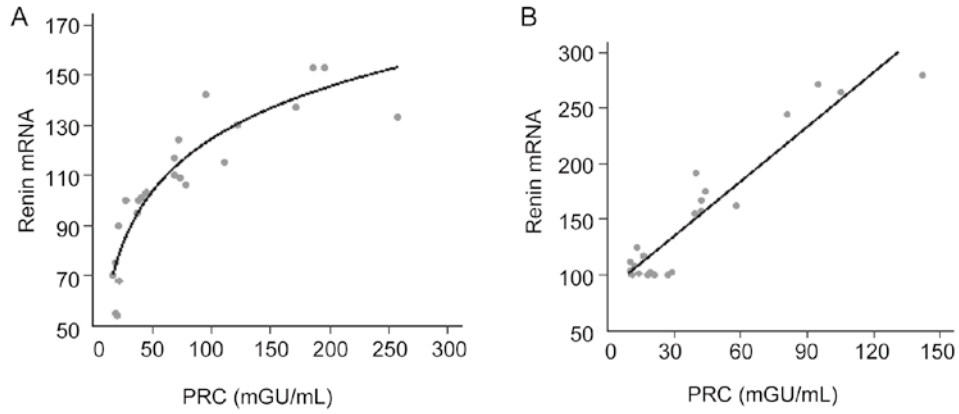

Fig. 7. Correlations between PRC and renin mRNA level in the right kidney (*A*, r^2=0.6708, P<0.0001) and in the hydronephrotic kidney (*B*, r^2=0.9067, P<0.0001)

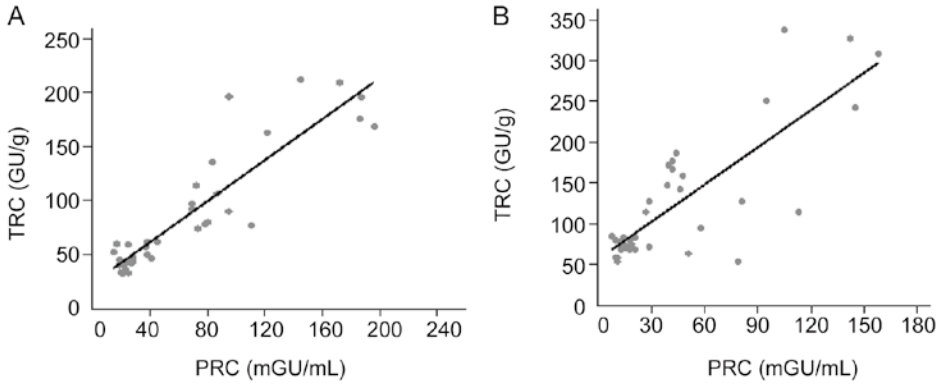

Fig. 8. Correlations between PRC and TRC from the right kidney (*A*, r^2=0.8185, P<0.0001) and the hydronephrotic kidney (*B*, r^2=0.6489, P<0.0001).

mRNA level in the right kidney (r^2=0.6708, P<0.0001, Fig. 7*A*) and in the hydronephrotic kidney (r^2=0.9067, P< 0.0001, Fig. 7*B*). Positive correlation relationships were also found between PRC and TRC from the right kidney (r^2=0.8185, P<0.0001, Fig. 8*A*) and the hydronephrotic kidney (r^2=0.6489, P<0.0001, Fig. 8*B*).

3 DISCUSSION

In the present study, we investigated the effects of enalapril, sodium loading, and the interaction of both treatments on renin synthesis and secretion in Balb/C mice with the left hydronephrotic kidney. In all cases, we found that PRC in blood from the hydronephrotic renal vein was lower than that from the contralateral renal vein, but similar to the level in the aorta, indicating that there was no net secretion from hydronephrotic kidney in which the structure of macula densa was destroyed. This phenomenon was consistent with our previous findings[12], implying that the macula densa is important for the control of renin secretion in the normal circumstances.

In this study, the animals with 7 d enalapril treatment showed a significant increase in PRC in the circulation. This result was consistent with previous studies[17], indicating that a week-long enalapril treatment could effectively alter plasma renin level. There was a positive relationship between PRC and renin mRNA level in both the right and hydronephrotic kidneys, indicating that a rise in renin concentration in the circulation was mainly related to the increase in renin synthesis in the kidney.

The mechanism whereby ACE inhibition increases the level of renin mRNA and the number of cells that express the renin gene is incompletely understood[13,14]. Enalapril is known to inhibit a negative feedback loop of Ang II on renin release and renin gene expression[15,16]. Interruption of the negative feedback loop by an ACE inhibitor may have contributed to the increase of renin gene expression. In the present study, both tissue renin and renin mRNA levels increased in the hydronephrotic kidney in mice treated with enalapril, indicating that the ACE inhibitor stimulates renin synthesis by mechanisms that do not involve the macula densa.

The present study investigated the effects of sodium loading on renin synthesis and secretion in the hydronephrotic animals. Administration of 9-fludrocortisone in saline drinking water caused a fall in basal level of plasma renin. Meanwhile the levels of tissue renin protein and renin mRNA decreased in the normal and hydronephrotic kidneys. These results are the reverse of the rise with a low sodium intake in the previous study in which PRC and renin mRNA increased significantly[16]. However, in enalapril-treated mice, sodium loading attenuated the response in TRC and renin mRNA level in both the hydronephrotic and contralateral kidneys compared with enalapril-treated mice alone. These results suggest that sodium loading acts directly on renin synthesis. In many physiological conditions several signals act simultaneously on the juxtaglomerular (JG) cells, which must process the information and produce an integrated response. However, the net response to the stimulatory and/or inhibitory signals is not always predictable.

Renin release is modulated by the factors such as plasma sodium, Ang II, the renal nerves and renal baroreceptor[17,18]. An increased delivery of sodium to the macula densa inhibits renin release[19-21]. The present study showed that sodium loading reduced renin synthesis in the hydronephrotic and contralateral kidneys, indicating that the synthetic procedure might not require the macula densa to be present. It appears that sodium may act directly on the JG cells or

through some other humoral factors. The suppression of the renin-angiotensin-aldosterone system after saline infusion might have been mediated in part by the increase in atrial natriuretic peptide (ANP) secretion[22-24].

The effects of chronic sodium loading on renal function and long-term blood pressure control have been discussed[25,26]. Studies have suggested that excessive sodium intake can cause renal injury and abnormal kidney function[27,28]. Furthermore, the salt-sensitive hypertension would be related to an inappropriate regulation of the RAS, which is known to have an important role in long-term blood pressure regulation[29-31].

In conclusion, these results demonstrate that renin synthesis is stimulated by converting enzyme inhibition in the presence or absence of the functional macula densa. Sodium loading reduces renin synthesis in the kidney in which the response is independent of the macula densa. High sodium intake is a potent regulator decreasing renin synthesis and secretion. The mechanisms of the interaction between the factors need to be further evaluated, but it is possible that both enalapril and high sodium intake could lead to a balance in renin synthesis and secretion in the hydronephrotic kidney with subsequent damage of the renal function.

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