

ORIGINAL ARTICLE

Effect of low sodium intake and β -blockade on renin synthesis and secretion in mice with unilateral ureteral ligation

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We previously reported that sodium depletion increased renin secretion from the normal kidney in mice. We postulated that the combined procedures of sodium depletion and β -adrenoceptor blockade would affect the activity of the renin–angiotensin system. To test this hypothesis, we investigated the interaction of low sodium intake (LSI) and propranolol (PRO) on renin synthesis and secretion. To prevent the influence of tubule flow on renin secretion, mice with a left hydronephrotic kidney were used. LSI increased plasma renin concentration (PRC) 5.6-fold in the right renal vein ($P < 0.01$). There was no net increase of PRC in the left renal vein. Tissue renin concentration (TRC) was elevated 3.6-fold and 1.3-fold in the right and left kidneys ($P < 0.01$), respectively. After administration of PRO, PRC decreased by 34% in the right renal vein and 47% in the aorta ($P < 0.05$); TRC was reduced by 37.5% in the right and 29.3% in the hydronephrotic kidneys ($P < 0.05$). The combination of LSI and PRO increased PRC 3.4-fold and 1.8-fold in the right ($P < 0.01$) and left renal veins ($P < 0.05$), respectively. TRC increased 3.4-fold in the right ($P < 0.01$) but only 61% in the left kidneys ($P < 0.05$). The pattern in change of renin mRNA levels was similar to TRC but the absolute amount was smaller. There were correlations between PRC and renin mRNA, and between TRC and renin mRNA in both kidneys ($P < 0.001$). Thus, LSI increased renin synthesis in both kidneys. However, there was no apparent renin secretion in the hydronephrotic kidney. PRO treatment suppressed renin synthesis and renin secretion, irrespective of hydronephrosis and LSI. The macula densa is critical for renin secretion under all of the circumstances studied. *Hypertension Research* (2010) 33, 1258–1263; doi:10.1038/hr.2010.167; published online 30 September 2010

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INTRODUCTION

It is generally accepted that the circulating renin–angiotensin–aldosterone system is involved in the control of total body sodium. However, changes in sodium balance cause major alterations in renin secretion. This may be a direct effect of sodium delivery to the macula densa cells, or an indirect action mediated by neural or humoral signals induced by the alteration in extracellular sodium concentration or fluid volume.^{1–3}

Of the hypotheses proposed for the regulation of renin secretion by sodium, the macula densa theory has received most attention.^{4–6} In the murine macula densa cell line MMDD1, an increase in intracellular sodium chloride reduces the effect of salt restriction on tubuloglomerular feedback and renin secretion.⁶ In normal subjects during slow sodium loading, a volume receptor elicited reduction in renal nervous activity via β_1 -adrenoceptors decreases renal tubular sodium reabsorption proximal to the macula densa, leading to increased NaCl concentration at the macula densa and subsequent inhibition of renin secretion.⁷ A low sodium diet stimulates renin secretion from the

kidney in dogs.⁸ However, the role of the macula densa in the regulation of renal renin synthesis and secretion remains unclear.^{8,9} The response in renin secretion is known to be the result of multiple interactions.¹⁰

Studies have demonstrated that β -adrenergic agonists increase renin release.^{11–14} A moderate increase in the renal sympathetic nerve activity produced by graded common carotid occlusion also stimulates renin secretion. This increase was prevented by β -adrenoceptor blockade or surgical denervation of the kidney.^{15,16} In mice, the release of renin from dense-core vesicles of juxtaglomerular granular cells in the kidney was modulated by normal rates of catecholamine release from the sympathetic nerve terminals.¹⁷ In renally denervated rats, an enhanced sensitivity of the α_1 -adrenoceptors to adrenergic agonists and an increase of AT1 receptor functionality in the renal vasculature were observed, suggesting an interaction between the sympathetic nervous system and the renin–angiotensin system in terms of a crosstalk relationship.¹⁸ An increase in the renal sympathetic nervous activity was correlated with an increase in the renal

renin-angiotensin system content in low-salt-treated rats.¹⁹ However, the exact mechanism of the regulation of renin secretion and synthesis by sodium and adrenoceptors is not fully understood. The aim of this study was to examine the interaction of β -adrenoceptor blockade and low sodium intake (LSI) on renin synthesis, and secretion in mice with a hydronephrotic kidney.

METHODS

Animals and experimental protocol

In all, 40 male Balb/C mice, aged 10 weeks, were used in this study. The experiments were conducted according to the guidelines of the National Research Council and were approved by the local ethics committee. All mice weighing 25–30 g were subjected to left ureteral ligation. They were anesthetized by intraperitoneal injection of 60 mg kg⁻¹ sodium pentobarbitone. The left kidney was exposed by a flank incision and the ureter was doubly ligated with 1.0 silk suture. Antibiotic powder (cicatin, containing zinc bacitracin and neomycin sulfate) was dusted in the abdominal cavity, and the incision was closed. Surgery time was 10–15 min per animal. The mice were maintained on a standard laboratory diet and had free access to tap water. At 4 weeks after the operation, the left kidney was hydronephrotic.^{20,21} At this time the following studies were performed. The control group ($n=10$) were fed regular mouse diet. The LSI ($n=10$) group were fed a low sodium diet (0.1% NaCl) and injected with frusemide (2 mg) on day 1. The propranolol (PRO, $n=10$) group were given PRO 12 mg kg⁻¹ per day in drinking water. The combined procedure group (LSI+PRO, $n=10$) were treated with LSI and PRO. The experimental procedure was carried out in the four groups for 2 weeks.

At 2 weeks after the experimental intervention started, the mice were anesthetized and both the kidneys were exposed through a midline incision. Briefly, a blood sample (20 μ l) was taken from the left and right renal veins and from the abdominal aorta.^{20–22} Plasma was separated from each blood sample by microcentrifuge. After blood sampling, the mouse was immediately killed. The right and left kidneys were removed and divided into two along their longitudinal plane. One half was used to determine the renal renin concentration and the other for renin mRNA.

Measurement of blood pressure (BP)

Mean arterial pressure was recorded every 2 days before and throughout the experiment in conscious mice, by the tail cuff method as described previously.²²

Measurement of plasma renin concentration (PRC) and tissue renin concentration (TRC)

PRC was measured in the blood from the aorta and renal veins using a radioimmunoassay described previously.^{20–22} The renin value was expressed in Goldblatt units (1 GU=0.42 μ g of angiotensin I formation) per milliliter of plasma. The $\frac{1}{2}$ kidneys removed from each mouse were weighed and homogenized in 1 ml buffer. Aliquots (20 μ l) were used for renin measurement. Renin concentration was expressed in GU per gram of kidney weight and GU per kidney.

Measurement of renin mRNA in the kidney

Total RNA in the kidney was isolated using Trizol reagent (Invitrogen, Grand Island, NY, USA) according to the manufacturer's instructions. The amount of RNA isolated was measured by absorbance at 260 nm. An aliquot of each sample of RNA was diluted in 20 \times standard saline citrate (3 mol l⁻¹ NaCl, 0.3 mol l⁻¹ sodium citrate) and denatured in formaldehyde. The dot-blot hybridization for measuring renin mRNA in the total RNA sample was carried out as described previously.^{20–22} To analyze the value of renin mRNA between kidneys, the results from the renin signal were expressed relative to a value of 100 U in the control kidney. The mRNA was then referred back to the tissue weight of the sample, as described previously.^{20–22}

Statistical analysis

Statistical analysis was performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Data are presented as the mean \pm s.e.m. Unpaired *t*-test was used to compare two values between different groups of animals. Multiple groups were

analyzed with analysis of variance followed by *post-hoc* test. The linear regression between PRC, TRC and renin mRNA levels was analyzed with PEMS 3.1 for Windows. $P<0.05$ was considered significant.

RESULTS

All mice were in good condition, and at the end of the experiments there were no differences in body weights between animals. BP did not differ among the groups after unilateral ureteral ligation. In the 2 weeks of LSI, BP did not change. However, PRO treatment lowered BP in mice (Figure 1). In animals treated with LSI and PRO together, BP did not significantly change, indicating that there might be a complex response between these two procedures on BP in the hydronephrotic mouse model.

Changes in kidney weights

In mice with left ureteral ligation, all left kidneys were hydronephrotic. During postmortem, liquid in the left kidneys was removed and the kidneys were weighed. In control mice the right kidney weighed 0.26 \pm 0.05 g and left hydronephrotic kidney 0.12 \pm 0.02 g ($P<0.01$). In LSI mice, the right kidney weights were 0.21 \pm 0.02 g and the left kidney weights were significantly lower at 0.10 \pm 0.01 g, ($P<0.01$). In both PRO and PRO+LSI groups, the left hydronephrotic kidney weights were also lower than the contralateral kidney. Light microscopy confirmed that the tissue in the left hydronephrotic kidney was much thinner than that in the contralateral kidney, resulting in the reduction of the left kidney weight.

PRC in the aorta and renal veins

PRC in blood from the aorta and from both the right and left renal veins was measured with radioimmunoassay. In control animals PRC was 26.7 \pm 2.6 mGU ml⁻¹ in the aorta, 37.2 \pm 3.0 mGU ml⁻¹ in the right renal vein and 27.7 \pm 2.4 mGU ml⁻¹ in the left renal vein draining the hydronephrotic kidney. The value in the left renal vein was lower than in the right renal vein ($P<0.05$, Figure 2). In LSI mice treated with low sodium diet and frusemide injection, PRC rose to 166.8 \pm 30.4 mGU ml⁻¹ in the aorta ($P<0.01$) and 247.1 \pm 32.8 mGU ml⁻¹ in the right vein, an increase of 5.6-fold,

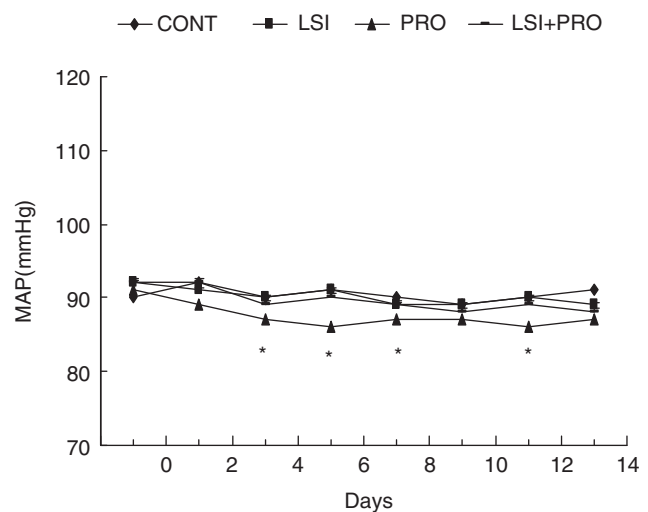


Figure 1 Effects of low sodium intake (LSI), propranolol (PRO) and LSI+PRO on mean arterial pressure (MAP) in mice ($n=10$ each group). Data are mean \pm s.e.m. * $P<0.05$. CONT, control.

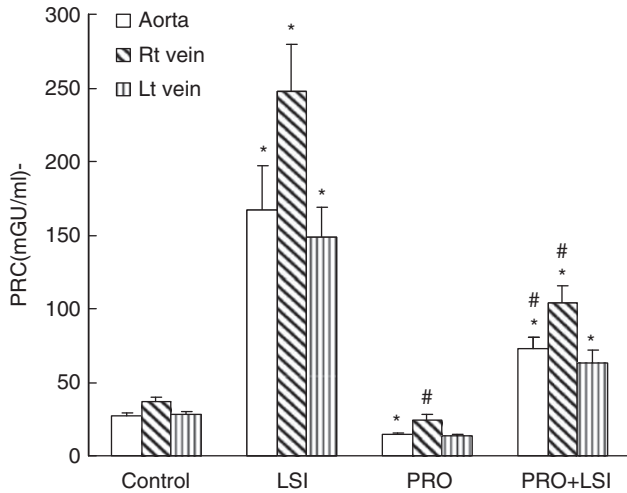


Figure 2 Plasma renin concentration (PRC) in the aorta, right (Rt) and left (Lt) renal veins in four groups of mice ($n=10$ each group, the left ureteral ligation was performed in all mice) after treatment with low sodium intake (LSI), propranolol (PRO) and LSI+PRO. Data are expressed as mean \pm s.e.m. * $P<0.05$ vs. control; # $P<0.05$ vs. LSI group. GU, Goldblatt unit.

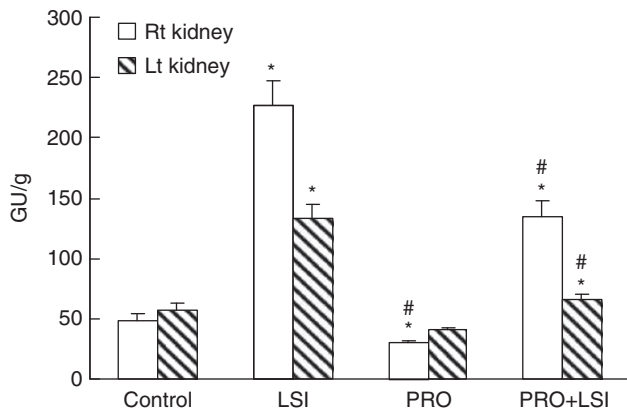


Figure 3 Tissue renin concentration in the right (Rt) and left (Lt) hydronephrotic kidneys in mice treated with low sodium intake (LSI), propranolol (PRO) and LSI+PRO. $n=10$ each group. Values are mean \pm s.e.m. * $P<0.05$ vs. control; # $P<0.05$ vs. LSI group.

which was higher than the value in the aorta ($P<0.01$). The value in the left renal vein did not differ from that in the aorta. In PRO mice treated with PRO, PRC was decreased to 14.1 ± 1.3 mGU ml $^{-1}$ in the aorta, 24.5 ± 3.4 mGU ml $^{-1}$ in the right renal vein and 13.9 ± 1.1 mGU ml $^{-1}$ in the left renal vein. In LSI+PRO mice, PRC was 72.4 ± 7.7 , 103.9 ± 11.6 and 63.1 ± 8.7 mGU ml $^{-1}$ in the aorta, right and left renal veins, respectively, an increase of 1.3- to 1.8-fold ($P<0.01$) compared with the value in control group. However, all values in LSI+PRO mice were less than in mice treated with LSI alone ($P<0.01$, Figure 2). The data showed there was no net increase of PRC in the hydronephrotic kidneys. LSI increased PRC levels from the right kidneys, whereas PRO treatment reduced PRC levels from the right organs. Thus PRO can attenuate renin secretion stimulated by LSI.

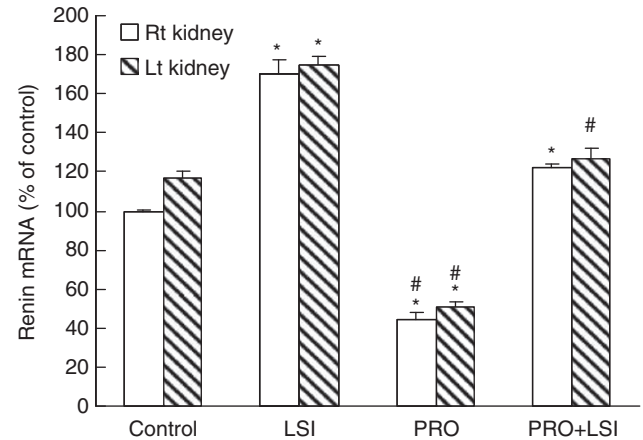


Figure 4 Renin mRNA levels in the right (Rt) and left (Lt) hydronephrotic kidneys. Renin mRNA expressed as a percentage of the value in the normal kidney in control mice. Animals were treated with the following procedures: control, low sodium intake (LSI), propranolol (PRO) and LSI+PRO. $n=10$ each group. Values are mean \pm s.e.m. * $P<0.05$ vs. control; # $P<0.05$ vs. LSI group.

TRC in both kidneys

TRC was measured in both kidneys with radioimmunoassay. TRC was 48.8 ± 5.2 GU g $^{-1}$ in the right and 57.4 ± 4.9 GU g $^{-1}$ in the left hydronephrotic kidneys in the control mice (Figure 3). In LSI mice, TRC was increased to 227.3 ± 19.8 GU g $^{-1}$ in the right kidney and to 133.9 ± 11.3 GU g $^{-1}$ in the left ($P<0.001$). In PRO mice, TRC was decreased to 30.5 ± 1.4 GU g $^{-1}$ in the right kidney and 40.6 ± 2.1 GU g $^{-1}$ in the left. There was a significant change in values in both kidneys compared with the control ($P<0.05$). In LSI+PRO mice, TRC was 134.1 ± 13.9 GU g $^{-1}$ in the right kidney and 65.4 ± 4.8 GU g $^{-1}$ in the left hydronephrotic kidneys, an increase of 3.4-fold and 61%, respectively, compared with the PRO alone group ($P<0.01$). There was also a significant difference in TRC in both kidneys between LSI+PRO and LSI alone ($P<0.01$). PRO had a depressive effect on renin levels during sodium depletion and in the presence or absence of hydronephrosis. The results showed that there was an interaction between sodium depletion and PRO on renin production in the kidneys. When the values were expressed per kidney (data not shown) the response was similar to that expressed per gram of kidney weight.

Renin mRNA levels in both kidneys

The change in renin mRNA levels in the kidney was assessed by dot-blot quantification. The results from four groups are shown in Figure 4. In control mice, renin mRNA was 100 U g $^{-1}$ in the right kidney and 116.4 ± 3.9 U g $^{-1}$ in the hydronephrotic kidney ($P<0.05$). In LSI group, the value of renin mRNA was 169.8 ± 7.9 U g $^{-1}$ ($P<0.01$) in the right normal kidney and 175.0 ± 4.1 U g $^{-1}$ ($P<0.001$) in the hydronephrotic kidney. In PRO group, renin mRNA level decreased from the control level to 44.1 ± 3.7 U g $^{-1}$ ($P<0.001$) in the right kidney and to 50.6 ± 3.0 U g $^{-1}$ in the hydronephrotic kidney ($P<0.001$). In LSI+PRO mice, renin mRNA level was 122.3 ± 2.1 U g $^{-1}$ ($P<0.05$) in the right and 127.0 ± 5.1 U g $^{-1}$ ($P<0.01$) in the left hydronephrotic kidneys, a decrease of 27% of the levels in both kidneys compared to mice in the LSI group.

Linear regression analysis showed that there was positive correlation between PRC and renin mRNA level in the right kidney ($r^2=0.5723$,

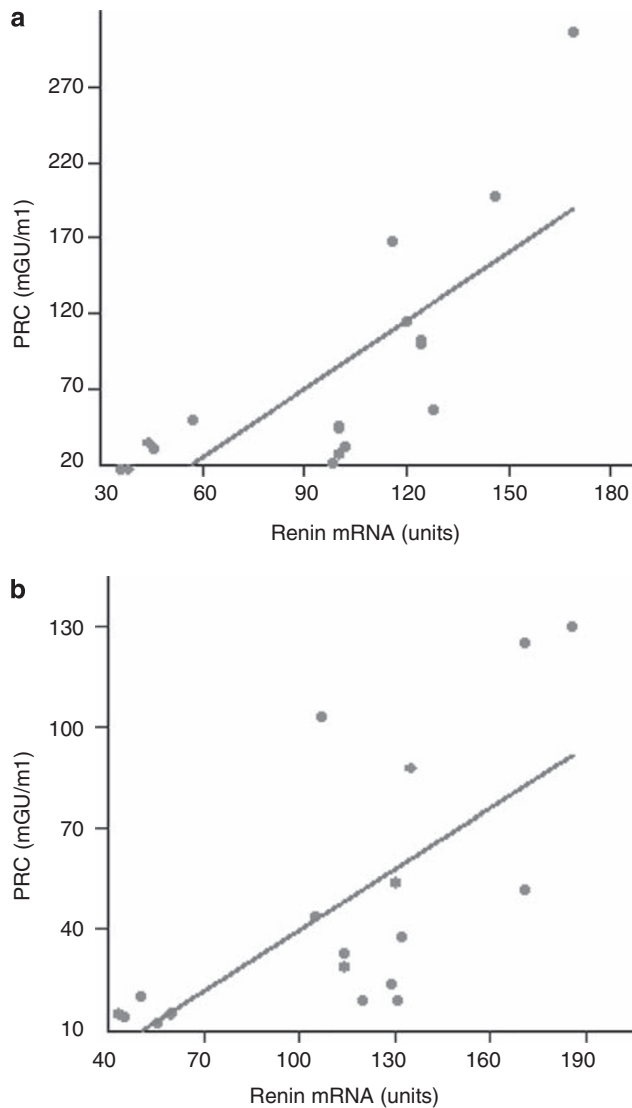


Figure 5 Correlation between plasma renin concentration (PRC) and renin mRNA levels induced by the different procedures in the right (**a**, $r^2=0.5723$, $P<0.001$) and left hydronephrotic kidneys (**b**, $r^2=0.4746$, $P<0.01$). $n=40$. GU, Goldblatt unit.

$P<0.001$, Figure 5a) and in the left hydronephrotic kidney ($r^2=0.4746$, $P<0.01$, Figure 5b). Meanwhile, a positive correlation was seen between TRC and renin mRNA in the right kidney ($r^2=0.7117$, $P<0.001$, Figure 6a) and in the left hydronephrotic kidney ($r^2=0.6146$, $P<0.001$, Figure 6b). These results show that the change of renin gene expression in the kidney is paralleled with PRC and TRC in mice treated with LSI and PRO. Again, there was a significant interaction between LSI and PRO on renin synthesis and secretion.

DISCUSSION

In the previous study, when the left ureter of mice was ligated the kidney became hydronephrotic and lost all of its tubular structure, so that it primarily consists of an arteriole system and glomeruli.²¹ In this study, an assessment of the secretion level was carried out by measuring the concentration of renin in the right, left renal veins and aorta. It

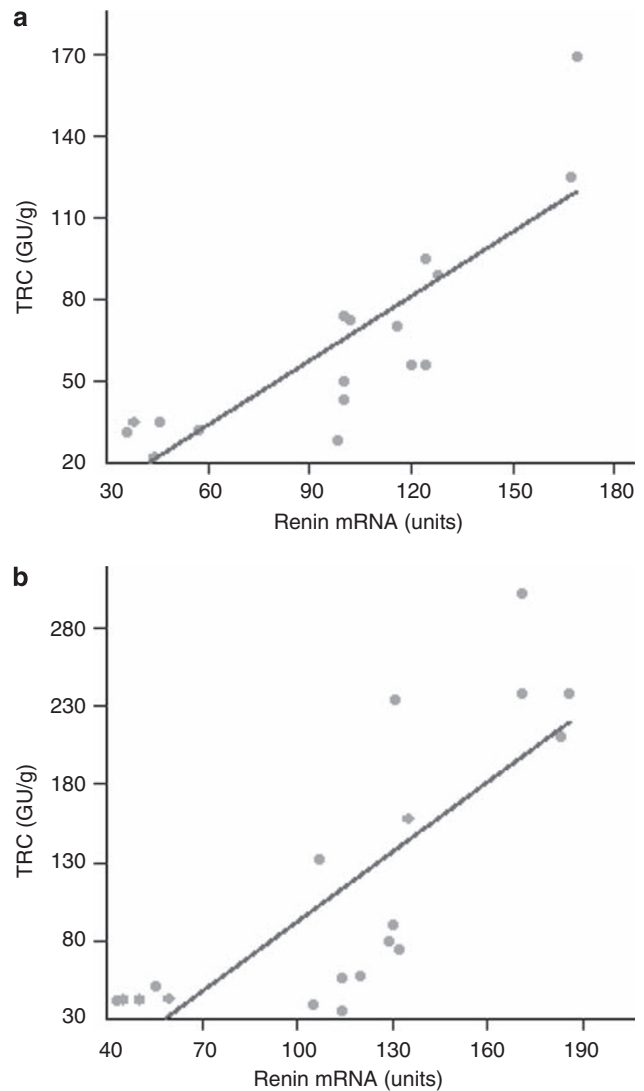


Figure 6 Correlation between tissue renin concentration (TRC) and renin mRNA levels caused by the different treatments in the right (**a**, $r^2=0.7117$, $P<0.001$) and left hydronephrotic kidneys (**b**, $r^2=0.6146$, $P<0.001$). $n=40$. GU, Goldblatt unit.

does enable us to say whether there was either net secretion or net removal of renin as the blood traverses the kidney structure. In the control state, there was no net secretion of renin in the hydronephrotic kidney. Even the powerful procedure of LSI and furosemide administration was unable to provide a net increase of PRC in the left renal vein, suggesting that the hydronephrotic kidney apparently ceased to secrete renin. Thus the macula densa has a pivotal role for renin to be released following chronic stimulation. However, a LSI caused a rise in TRC and renin mRNA levels in both the normal and the hydronephrotic kidneys, suggesting that the macula densa may be not critical for renin synthesis stimulated by sodium depletion.

There have been a number of studies on the effect of sodium on renin release but the mechanism by which sodium alters renin secretion is unclear.^{23–28} Renin secretion can be influenced by the flow and/or composition of fluid at the macula densa.^{29–31} In some studies, the tubule was perfused with different concentrations of sodium chloride

and the renin release measured.^{32,33} When a solution of high sodium chloride composition was given, renin release was lowered. These studies support the concept that renin secretion is regulated by the macula densa. However, it has been reported that the renin secretion, stimulated by the diuretic ethacrynic acid, is independent of the presence of Na⁺, Cl⁻ and Ca⁺⁺.³⁴ There can be little doubt that the macula densa is important in the regulation of renin release, but the role of the macula densa in the control of renin synthesis remains unclear. This study showed that sodium depletion increased renin synthesis in the hydronephrotic kidney in which there was no macula densa.

Activation of renal β -adrenoceptors stimulates renin release and mediates increased renin secretion rate when renal nerves are electrically stimulated.^{27,35–38} The administration of β -adrenergic antagonists could block the increase in renin secretion, but there has been a certain amount of variation in the results reported.^{26,39} β -adrenoceptor blockade reduced basal level of plasma renin activity in human subjects and experimental animals.^{17,40} This study showed that PRO caused a fall in the PRC, indicating that adrenergic stimulation of renin release is present under normal conditions. The administration of PRO in the sodium-depleted animals reduced the increment in PRC stimulated by LSI, suggesting that there is an interaction between sodium depletion and PRO on renin secretion in the kidney. The results also showed that there was no net secretion of renin in the hydronephrotic kidney under the circumstances either PRO alone or the combined procedure with sodium depletion. This further demonstrated that the macula densa has a critical role in the regulation of renin secretion.

To determine the effects of sodium depletion and PRO on renin synthesis, TRC and renin mRNA levels were measured in the kidney. In mice with LSI, TRC and renin mRNA levels were elevated in both the normal and hydronephrotic kidneys. When PRO was given to sodium depleted mice the levels of TRC and renin mRNA levels were reduced compared with the animals with LSI alone, indicating that β -adrenergic blockade attenuated the effect of sodium depletion on renin synthesis. The results demonstrated that there is an interaction between PRO and LSI on TRC and renin mRNA levels. On the other hand, PRC in LSI- and PRO-treated mice was lower than that with LSI alone. Furthermore, linear regression analysis showed that there was a positive correlation between levels of PRC, TRC and renin mRNA in both normal and hydronephrotic kidneys, indicating that there is an interaction between LSI and PRO on renin synthesis and secretion. As renin secretion is affected, additional post-translational interactions or an effect of β -adrenoceptor blockade at the level of the secretory pathway may occur in the kidney. Thus β -adrenoceptors have an important role in renin secretion stimulated by LSI.

In conclusion, in the hydronephrotic kidney, there was no net increase in renin secretion because of the lack of macula densa under all of the circumstances studied. The macula densa is critical for renin secretion but not for the stimulation of renin synthesis. There is an interaction between sodium depletion and β -adrenoceptor blockade on renin synthesis and secretion. These results probably reflect the combined effect of the reduced tonic stimulation by sympathetic transmitter release and of sodium depletion.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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