EFFECTS OF RENAL DENERVATION ON PRESSURE-NATRIURESION IN SPONTANEOUSLY HYPERTENSIVE RATS

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To investigate the role of renal sympathetic nerve activity (RSNA) under developing and established hypertension, renal function was studied in chronically renal-denervated and sham-operated male spontaneously hypertensive rats (SHR) and control Wistar Kyoto rats (WKY) at 8 (early hypertensive) and 22 (established hypertensive) weeks of age. To further characterize the renal pressure-natriuresis-diuresis relationship in SHR, renal perfusion pressure (RPP) was reduced by aortic constriction to the level seen in age-matched WKY and the same studies were repeated. After denervation, urinary sodium excretion (U\textsubscript{Na}\textsubscript{V}), fractional excretion of sodium (\textit{FE}\textsubscript{Na}) and urine flow (UF) were increased in 8-week-old SHR (\textit{p}<0.01). With the exceptions of U\textsubscript{Na}\textsubscript{V} and \textit{FE}\textsubscript{Na} in denervated 8-week-old SHR, renal cortical blood flow, glomerular filtration rate, UF, U\textsubscript{Na}\textsubscript{V} and \textit{FE}\textsubscript{Na} decreased with the reduction of RPP in all of the SHR groups. These results suggest that RSNA significantly influences renal sodium and fluid handling, thus contributing to the shifting of the arterial pressure-renal sodium excretion curve to the right along the pressure axis and/or to an increase in the steepness of the relationship in 8-week-old SHR. There appeared to be a marked difference in renal sodium handling between 8- and 22-week-old SHR. 

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The hypothesis proposed by Guyton and associates that the kidney plays a dominant role in the long-term control of arterial pressure is based on the pressure-diuresis-natriuresis phenomenon. It is not yet clear how renal sympathetic nerve activity (RSNA) influences the pressure-natriuresis-diuresis curve and the development and maintenance of hypertension. Renal denervation and nerve stimulation studies in spontaneously hypertensive rats (SHR) have provided little insight as to whether the neural effects are due to neurotransmitters or electrical activity at the nerve terminals, or are secondary to changes in the renin-angiotensin system or other humoral factors. Although RSNA is important in the regulation of renal renin secretion, the mechanisms involved remain to be clarified. It has been reported that once hypertension is established, RSNA does not play a significant role in the maintenance of increased blood pressure in SHR. In contrast, some investigators have speculated that an abnormality in the kidney itself is involved in the development of hypertension in SHR.

We hypothesized that RSNA plays an important role in the pathogenesis of hypertension by shifting the pressure-natriuresis curve to the right along the pressure axis and/or by increasing the steepness of the relationship, and that the role of RSNA differs in developing and established hypertension in SHR. To evaluate these hypotheses, we

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examined renal hemodynamics and excretory function in chronically renal-denervated SHR and matched Wistar Kyoto rats (WKY), as well as in sham-operated SHR and matched WKY at 8 (early hypertensive) and 22 (established hypertensive) weeks of age. To further characterize the renal pressure-diuresis-natriuresis relationship in SHR, we reduced the mean renal perfusion pressure (RPP) to the level in age-matched WKY by aortic constriction (AC), and again studied renal hemodynamics and excretory function by the same methods.

MATERIALS AND METHODS

Animal Preparation

Male SHR at 7 and 21 weeks of age and sex- and age-matched WKY were used. The rats were bred with siblings in our laboratory from original stock which was kindly donated by Dr. Kozo Okamoto (Department of Pathology, Kinki University, Osaka, Japan). Animals were housed in a temperature-controlled room that was maintained on a 12 h light-dark cycle. They were provided with standard rat chow and tap water ad libitum. A total of 51 SHR were subjected to bilateral renal denervation (7 weeks: n=14, 21 weeks: n=13) or sham operation (7 weeks: n=12, 21 weeks: n=12). Their WKY counterparts were also subjected to bilateral renal denervation (7 weeks: n=10, 21 weeks: n=10) or sham operation (7 weeks: n=10, 21 weeks: n=11) 1 week before the clearance experiments. Under ether anesthesia, renal denervation was accomplished through a ventral incision by stripping the renal adventitia and painting both the renal arteries with 10% phenol (wt/vol) in absolute ethanol. The sham operation consisted of ventral incision and isolation of the kidneys from adjacent tissues. Surgical procedures were conducted aseptically, and the animals received penicillin after each procedure to prevent infection.

Experimental Protocol

One week after renal denervation or the sham operation, the clearance experiment was performed on these animals, which were then 8 and 22 weeks old. Immediately after the induction of sodium pentobarbital anesthesia (50 mg/kg, intraperitoneally), the rats were placed on their backs with their limbs gently extended, and taped into position. They were allowed to breathe spontaneously. The femoral artery and vein were cannulated with polyethylene tubing (PE-50): the artery was used for arterial pressure measurement and arterial blood sampling, and the vein was used for continuous intravenous infusion. The bladder was cannulated with soft tubing (PE-90). Femoral arterial pressure was used as an approximation of RPP. An adjustable constrictor clamp was placed around the abdominal aorta just above the renal arteries to alter RPP. The surface of the left kidney was exposed with the aid of retractors through an abdominal incision. An H2-sensitive platinum electrode (0.08 mm in diameter) was inserted into the parenchyma of the left kidney to a depth of 1 mm to measure renal inner cortical blood flow by the hydrogen washout method (PHG-201, Unique Medical Co., LTD., Tokyo, Japan). The electrode had calibration marks to facilitate its insertion to a known depth. A single calomel KCl bridge, held against the exposed tissue of the leg, completed the circuit. The theory and application of the H2 washout method have been detailed by Aukland et al9 and Chapman et al10. The rats were maintained at a rectal temperature of between 37 and 38°C with infrared lamps. [3H] Inulin (2 μCi/ml) was added to 0.9% sodium chloride for the measurement of glomerular filtration rate (GFR). This solution was infused at a rate of 0.05 ml/min/100g body weight to induce mild saline diuresis. In general, supplemental doses of anesthetic were not required; an additional intravenous bolus of sodium pentobarbital was given as needed to maintain a stable RPP. With this procedure, changes in blood pressure caused by pentobarbital anesthesia could be controlled satisfactorily. Urine was collected continuously after the start of the infusion, and a urine sample taken after 60–80 min was used as the control assay. In preliminary experiments, we confirmed that an equilibration time of 60 min was long enough to stabilize both cardio-renal function and the serum inulin concentration. At the midpoint of the clearance period, a small volume of H2 gas was applied using a face mask, and renal cortical blood flow (RCBF) was measured. Renal cortical vascular resist-
| TABLE I | RENAL PERFUSION PRESSURE, HEART RATE, BODY AND KIDNEY WEIGHTS IN 8- AND 22-WEEK-OLD SHR AND WKY |
|---------------------------------|---------------------------------|-----------------|---------------|-----------------|-----------------|
| Number of rats | 8-week-old SHR | 8-week-old WKY | 22-week-old SHR | 22-week-old WKY | 8-week-old SHR | 8-week-old WKY | 22-week-old SHR | 22-week-old WKY |
| Body wt (g) | 12 | 13 | 12 | 14 | 12 | 13 | 12 | 14 |
| Kidney wt (g) | 214±6* | 217±4* | 178±6* | 178±6* | 179±5* | 179±5* | 179±5* | 179±5* |
| Heart rate (beats/min) | 1.70±0.65 | 1.79±0.67 | 2.20±0.07 | 2.21±0.10 | 1.85±0.60 | 1.89±0.69 | 2.26±0.08 | 2.27±0.12 |
| Renal perfusion pressure (mmHg) | 300±14 | 297±14 | 139±3* | 140±3* | 124±3* | 122±3* | 383±17 | 384±16 |

Results are expressed as mean±SEM. WKY, Wistar Kyoto rats; SHR, spontaneously hypertensive rats; wt, weight; AC, aortic constriction. *p<0.01, compared with 8-week-old SHR.

Hormonal Assays
The frozen right kidney was homogenized in 0.4 N perchloric acid and centrifuged at 3000 rpm for 15 min at 4°C. After the elimination of protein, the supernatant was assayed for norepinephrine, epinephrine, and dopamine by high-performance liquid chromatography (Hitachi 638-300, Tokyo, Japan) with electrochemical detection and using the alumina absorption method as a pretreatment.

Statistical Analysis
Student's t-test for paired and unpaired variates was used to determine significance, if appropriate. Values are expressed as...
Fig. 1. Renal cortical blood flow (RCBF) and renal vascular resistance (RVR) in 8- and 22-week-old SHR before (CONTROL) and after aortic constriction (AC), and in age-matched WKY. Open column, sham-operated SHR; filled column, denervated SHR; striped column, sham-operated WKY; dotted column, denervated WKY. *, **, p<0.05 and 0.01 vs 8-week-old. †, ‡, ††, †‡, p<0.05 and 0.01 vs age-matched WKY. §, §§, p<0.05 and 0.01 vs sham-operated. Mean ± SEM and differences were considered significant at p<0.05.

RESULTS

Body weight, kidney weight, and the kidney to body weight ratio were similar between sham-operated and denervated SHR, as well as between sham-operated and denervated WKY, at 8 and 22 weeks of age (Table I). In both the sham-operated and denervated groups, SHR weighed less than age-matched WKY at 8 weeks of age, but there was no significant difference at 22 weeks. There was no significant difference in kidney weight and the kidney to body weight ratio between age-matched SHR and WKY in either the sham-operated or denervated group. Heart rate was not affected by denervation or AC and was similar in age-matched SHR and WKY. RPP was similar in the sham-operated and denervated SHR, as well as in the WKY counterparts, at both 8 and 22 weeks of age. RPP was elevated in each SHR age group as compared to age-matched WKY (Table I).

Effects of Aging

1) "Control" SHR (prior to AC) and WKY
RPP increased with age in all of the SHR and WKY groups regardless of renal denervation (Table I). There were no signifi-
significant changes in RCBF with aging in SHR. RVR was higher at 22 weeks than at 8 weeks in both sham-operated and denervated SHR (Fig. 1). GFR did not change significantly with age in SHR regardless of denervation. UF was higher in 22-week-old than in 8-week-old sham-operated SHR, but this difference was not significant in denervated SHR (Fig. 2). Urinary sodium excretion ($U_{Na}V$) was significantly increased in sham-operated SHR and decreased in denervated SHR with aging. Fractional excretion of sodium ($F_{Na}$) increased with age in sham-operated SHR. In contrast, there were no significant changes in $F_{Na}$ with aging in denervated SHR (Fig. 3). In WKY, RCBF, RVR, GFR, UF, $U_{Na}V$ and $F_{Na}$ did not change with age (Figs. 1–3).

2) SHR with AC

RPP in SHR was reduced by AC to the level seen in the age-matched WKY (Table 1). RCBF in sham-operated SHR with AC was lower at 22 weeks than at 8 weeks, while RCBF in denervated SHR with AC showed no changes with age. RVR increased with age in both sham-operated and denervated SHR with AC (Fig. 1). GFR decreased with age in sham-operated SHR with AC, but not in denervated SHR. UF was similar in both age groups of SHR with AC, regardless of denervation (Fig. 2). $U_{Na}V$ in denervated SHR with AC was lower in the older group, while it was decreased to a similar level at both ages in sham-operated SHR. With AC, $F_{Na}$ was similar at both ages in sham-operated SHR. However, in denervated SHR with AC, $F_{Na}$ was lower at 22 weeks than at 8 weeks (Fig. 3).

Comparison of Sham-operated SHR and Age-matched Sham-operated WKY

RCBF in SHR and WKY were not significantly different in either of the age groups. RCBF in both age groups of sham-operated SHR decreased with AC to less than that in age-matched WKY. RVR was higher in SHR than in WKY at both ages, both with and without AC (Fig. 1). There were no significant differences in GFR between sham-operated SHR and age-matched WKY at either 8 or 22 weeks of age before AC. With AC, GFR became lower in sham-operated SHR than in age-matched WKY at both ages. UF in sham-operate SHR at 8 weeks was similar to that in age-matched WKY before AC, but it was reduced by AC and became lower than that in WKY. At 22 weeks, UF in sham-operated SHR was greater than that in WKY, and was reduced by AC to the level in WKY (Fig. 2). $U_{Na}V$ in sham-operated SHR was similar to that in age-matched WKY before AC, but became lower than that in WKY at both ages with AC. $F_{Na}$ in sham-operated SHR was not significantly different from that in sham-operated WKY at both ages with or without AC (Fig. 3).
TABLE II HORMONAL DATA AFTER AORTIC CONSTRICITION IN SHR

<table>
<thead>
<tr>
<th></th>
<th>8-week-old</th>
<th>22-week-old</th>
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<tbody>
<tr>
<td></td>
<td>sham</td>
<td>denervated</td>
</tr>
<tr>
<td>Norepinephrine (n=8)</td>
<td>102.0±8.2</td>
<td>4.1±0.7$$^{tt}$$</td>
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<tr>
<td>(ng/g kidney wt)</td>
<td></td>
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<tr>
<td>Epinephrine (n=8)</td>
<td>10.0±3.0</td>
<td>13.2±4.3</td>
</tr>
<tr>
<td>(ng/g kidney wt)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine (n=8)</td>
<td>13.6±1.3</td>
<td>4.8±1.5$$^{tt}$$</td>
</tr>
<tr>
<td>(ng/g kidney wt)</td>
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Results are expressed as mean±SEM. wt. weight. $$^{tt}$$ p<0.01, compared with age-matched sham-operated SHR.

Comparison of Denervated SHR and Age-matched Denervated WKY

RCBF in denervated SHR was similar to that in age-matched WKY at both ages before AC, but was reduced in SHR of both ages by AC and became significantly lower than that in age-matched WKY. RVR was higher in denervated SHR than in age-matched WKY before AC. With AC, although RVR was still higher in 8-week-old SHR than in age-matched WKY, it was decreased in 22-week-old SHR and was not significantly different from that in age-matched WKY (Fig. 1). There was no significant difference in GFR between SHR and age-matched WKY at each age before AC, but GFR became lower in SHR than in age-matched WKY at both ages with AC. There was no significant difference in UF between denervated SHR and age-matched WKY at both ages, with or without AC (Fig. 2). At 8 weeks of age, $U_{Na}V$ was higher in denervated SHR than in age-matched WKY both before and after AC. At 22 weeks of age, there was no difference in $U_{Na}V$ between SHR and WKY before AC, but $U_{Na}V$ became lower in SHR than in WKY with AC. At 8 weeks of age, $FE_{Na}$ was higher in denervated SHR than in age-matched WKY both before and after AC. In 22-week-old animals, there were no significant differences in $FE_{Na}$ between SHR and WKY with or without AC (Fig. 3).

Effects of Bilateral Renal Denervation on the "Control" SHR (prior to AC) and WKY

RCBF, RVR and GFR were not significantly changed by renal denervation in either of the SHR age groups (Figs. 1, 2). UF increased with denervation in 8-week-old SHR, but did not change in 22-week-old SHR (Fig. 2). $U_{Na}V$ and $FE_{Na}$ were significantly increased in 8-week-old SHR by renal denervation, but were not changed at 22 week (Fig. 3). RCBF, RVR, GFR, UF, $U_{Na}V$ and $FE_{Na}$ were not changed in either of the WKY age groups by renal denervation (Figs. 1–3).

Effects of AC on Sham-operated and Denervated SHR

RCBF, RVR, GFR, UF, $U_{Na}V$ and $FE_{Na}$ were significantly decreased in all of the SHR groups by AC, together with the acute normalization of RPP, except that RVR, $U_{Na}V$ and $FE_{Na}$ were not decreased in 8-week-old denervated SHR (Figs. 1–3).

In the comparison of denervated and sham-operated SHR with AC, RCBF, RVR and GFR were similar in both age groups (Figs. 1, 2). On the other hand, UF with AC in denervated SHR in both age groups was higher than that in their sham-operated counterparts (Fig. 2). At 8 weeks of age, $U_{Na}V$ and $FE_{Na}$ with AC were higher in denervated SHR than in sham-operated SHR. At 22 weeks of age, $U_{Na}V$ was higher in denervated SHR than in sham-operated SHR, but $FE_{Na}$ showed no significant difference between denervated and sham-operated SHR with AC (Fig. 3).

Hormonal Data after AC (Table II)

The renal norepinephrine and dopamine concentrations were significantly decreased by renal denervation at both 8 and 22 weeks.

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DISCUSSION

The current study demonstrated several differences in renal hemodynamics and excretory function between 8- and 22-week-old SHR. These findings suggest that RSNA works in a different fashion during the developing and established phases of hypertension in SHR. Of particular interest is the difference between the two SHR age groups in renal sodium handling at different RPP, with or without renal sympathetic innervation. \( \text{FE}_{\text{Na}} \) and \( \text{U}_{\text{Na}} \text{V} \) in SHR were significantly increased by renal denervation at 8 weeks, but not at 22 weeks. In each WKY age group, renal denervation had no effect on \( \text{U}_{\text{Na}} \text{V} \) or \( \text{FE}_{\text{Na}} \).

Comparison of sham-operated SHR and age-matched WKY showed no difference in \( \text{U}_{\text{Na}} \text{V} \) or \( \text{FE}_{\text{Na}} \) before AC. With AC, \( \text{U}_{\text{Na}} \text{V} \) in SHR became significantly lower than that in age-matched WKY while \( \text{FE}_{\text{Na}} \) was not significantly different. However, \( \text{FE}_{\text{Na}} \) in SHR itself was significantly reduced by AC at both ages. This indicates that the decrease in \( \text{U}_{\text{Na}} \text{V} \) in sham-operated SHR with AC resulted, at least in part, from the reduction in GFR, which was also significantly decreased with AC and which became lower than that in age-matched WKY. On the other hand, in a comparison of denervated SHR and WKY, \( \text{U}_{\text{Na}} \text{V} \) and \( \text{FE}_{\text{Na}} \) were significantly greater in SHR than in WKY at 8 weeks both before and after AC, while there was no difference at 22 weeks of age. These results suggest that RSNA works differently in 8-week-old SHR than in either age-matched WKY or 22-week-old SHR. The increase in \( \text{U}_{\text{Na}} \text{V} \) produced by renal denervation in 8-week-old SHR was considered to be derived from factors other than changes in GFR, because \( \text{FE}_{\text{Na}} \) was also increased while GFR was not changed significantly. This indicates that tubular function is modified by sympathetic denervation in 8-week-old SHR. One possible explanation for the change in tubular function is the direct effects of catecholamines on \( \alpha_1 \) receptors at renal tubules.\(^{12}\) On the other hand, RSNA has been reported to be related to the renin-angiotensin-aldosterone system (RAS), prostaglandins, vasopressin and other neurohumoral factors.\(^{13}\) These mechanisms may also be involved in the reduction of renal tubular sodium reabsorption. Regarding the RAS, Winternitz et al. reported that kidney tissue renin activity was similar in denervated (one week after renal denervation) and sham-operated SHR at 8 weeks.\(^{2} \) In a preliminary study, we reported that kidney tissue renin activity was similar in denervated (one week after renal denervation) and sham-operated SHR after AC at 8 and 22 weeks.\(^{14}\) These findings may indicate that the effects of renal denervation on sodium excretion in 8-week-old SHR did not result from suppression of the local intrarenal RAS. In addition, as we discuss later, dopamine is considered to be closely related to RSNA because it is a precursor of norepinephrine and epinephrine. Moreover, it has been reported that specific dopaminergic receptors are located at renal proximal tubules, which have been suggested to take part in renal sodium handling.\(^{15-18}\) Although the mechanism by which renal denervation increases natriuresis in 8-week-old SHR is not known, our results suggest that this phenomenon is peculiar to SHR at this age and may have great importance in the development of hypertension in this species.

\( \text{U}_{\text{Na}} \text{V} \) was not significantly reduced with the acute normalization of RPP in denervated SHR at 8 weeks, but was significantly reduced in sham-operated SHR. At 22 weeks, \( \text{U}_{\text{Na}} \text{V} \) was significantly decreased in both sham-operated and denervated SHR with AC. These findings, and the fact that \( \text{FE}_{\text{Na}} \) was decreased with AC in sham-operated SHR at 8 weeks, indicate that the reduction in \( \text{U}_{\text{Na}} \text{V} \) by AC in sham-operated SHR was caused by the change in GFR. We cannot strictly compare the pressure-natriuresis relationships in SHR and WKY because it was not possible to elevate RPP of WKY to the level observed in SHR physiologically. However, our study suggests the possibility that renal denervation changed the pressure-natriuresis relationship in 8-week-old, but not 22-week-old, SHR by shifting the curve to the left and/or by altering the steepness of the curve that relates renal arterial pressure to sodium excretion, as compared with that in age-matched WKY. It has also been suggested that renal tubular sodium reabsorption is significantly influenced by RSNA in SHR at this age. On the other hand, in 22-week-old SHR, \( \text{FE}_{\text{Na}} \) and \( \text{U}_{\text{Na}} \text{V} \) were both significantly decreased by
AC, but were hardly affected by renal denervation. This may indicate that acute normalization of RPP promotes sodium reabsorption at renal tubules in 22-week-old SHR, with very little, if any, influence of RSNA. Thus, RSNA appears to have substantially different effects on renal sodium handling in the 2 SHR age groups.

Rudd et al reported that acute renal denervation produces diuresis and natriuresis in 6-week-old SHR, but not in WKY. We evaluated the effects of chronic renal denervation in both 8- and 22-week-old SHR and WKY, and only our results at 8 weeks of age were compatible with their acute results concerning diuresis and natriuresis. The fact that renal denervation influenced renal sodium and water handling in 8-week-old SHR even in the chronic phase suggests that fluid and sodium retention resulted from augmented neurotransmitter release and/or tubular responsiveness in young SHR that were developing hypertension, not in older SHR (established hypertension). Rudd et al also reported that SHR kidneys at 6 weeks of age have a 43% higher concentration of norepinephrine than WKY at 6 weeks. These findings may indicate that augmented RSNA is involved in the pathogenesis of hypertension in SHR.

The significant reduction of the renal norepinephrine concentration to below 5% of that in sham-operated rats confirmed the completeness of renal denervation. The renal dopamine content was reduced to about one-third of that in sham-operated SHR, a finding compatible with that reported by Petrovic and Bell. Some investigators have reported that renal dopamine originates from several sources. Recent functional, biochemical, and morphological data have indicated the presence of dopaminergic sympathetic neurons among the renal nerves. Circulating free dopa is decarboxylated to dopamine by enzymatic activity in the tubular epithelium and conjugated plasma dopamine is also deconjugated to the free form as it passes through the renal circulation. It is well known that the stimulation of dopaminergic neurons, which may terminate on the efferent and afferent arterioles of the glomeruli and proximal tubules, increases urinary sodium excretion although the physiological role of renal dopaminergic innervation has not yet been clarified, an absence of dopaminergic innervation may cause a decrease of \( U_{Na} V \). On the other hand, it has been reported that urine dopamine is markedly greater than can be accounted for by filtered plasma dopamine. In the present study, it seems that the overall effects of the total loss of RSNA (including dopaminergic neurons) counteracted the expected effects of dopamine on renal sodium handling.

In conclusion, RSNA may influence sodium handling, thus contributing to the shifting of the arterial pressure-natriuresis curve to the right along the pressure axis and/or by increasing the steepness of the relationship in SHR. There was also a marked difference in sodium handling between SHR at 8 and 22 weeks of age. Our study indicates that RSNA may play an important role in the development of hypertension in SHR by influencing renal sodium handling.

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