Renal Nerve Contribution to NaCl-Exacerbated Hypertension in Spontaneously Hypertensive Rats

Wanida Sripairojthikoon, Suzanne Oparil, and J. Michael Wyss

Previous studies demonstrate that bilateral renal denervation enhances urinary sodium excretion and delays the onset of hypertension in young (7-week-old) spontaneously hypertensive rats (SHR) maintained on ordinary laboratory chow. We interpret these data as suggesting that increased renal nerve activity in this model contributes to hypertension by causing excess sodium retention. More recent studies show that dietary NaCl supplementation increases blood pressure and peripheral sympathetic nervous system activity in NaCl-sensitive SHR (SHR-S). The present study tests the hypothesis that the renal nerves contribute to the rise in arterial pressure caused by dietary NaCl supplementation in this model. SHR-S were fed a high (8%) or basal (1%) NaCl diet beginning at age 7 weeks. Bilateral renal denervation was carried out 2 weeks after the initiation of the diets, at which time systolic blood pressure was significantly higher in the high (compared with the basal) NaCl group. Systolic blood pressure was reduced slightly less in denervated SHR-S on the high (compared with basal) NaCl diet during the following 5 weeks. Renal denervation performed 1 week before initiation of the diets attenuated the subsequent development of hypertension equally in both groups. Both renal denervation and the high NaCl diet increased α2-adrenergic receptor numbers in the kidney; renal denervation caused an approximately equal increase in α2-adrenergic receptor binding in SHR-S on high and basal NaCl diets. The high NaCl diet increased plasma noradrenaline concentration, and renal denervation lowered mean arterial pressure but did not decrease circulating catecholamines in either diet group. Thus, the hypotensive effect of renal denervation in SHR-S is not dependent on a reduction of peripheral sympathetic nervous system activity. These data demonstrate that the renal nerves participate in the development of hypertension in SHR-S maintained on a basal or high NaCl diet, but the renal nerves do not appear to contribute significantly to the dietary NaCl-exacerbated component of hypertension in SHR-S. (Hypertension 1989;14:184–190)
development of hypertension in the dietary NaCl-loaded SHR-S by increasing both renal nerve activity and postsynaptic renal α2-adrenergic receptors.

In the current study, we tested this hypothesis by denervation of the kidneys of SHR-S either during the development of the NaCl-induced exacerbation of hypertension (experiment 1) or before dietary NaCl loading (experiment 2). Experiment 1 assessed the ability of renal denervation to reverse or attenuate the NaCl-induced exacerbation of hypertension in the SHR-S, while experiment 2 tested the ability of renal denervation to prevent the NaCl-induced effects. In both experiments, we also tested whether chronic NaCl diet or chronic renal denervation affected the number or binding affinity of renal α2-adrenergic receptors in SHR-S.

Materials and Methods

Male SHR-S were obtained from Taconic Farms, Germantown, New York (IBU3 colony) at 6 weeks of age. The rats were maintained on either a basal (1%) NaCl (diet 5001, Ralston Purina, Richmond, Indiana) or a high (8%) NaCl (diet 5883, Ralston Purina) natural food diet. Throughout the studies, rats were housed at constant temperature (24±1°C), humidity (60±5%), and 12-hour light/dark cycle (6:00 AM–6:00 PM). Food and tap water were available ad libitum throughout these experiments. During the metabolic studies, the food was mixed with 10% water to form a mash. Throughout the experiments, systolic blood pressure and heart rate were measured twice weekly from prewarmed unanesthetized rats by the indirect tail-cuff method. Body weight was also measured twice per week.

Bilateral renal denervations and bilateral sham operations were performed through flank incisions while the rats were under deep ether anesthesia. For renal denervation, the renal artery was separated from the renal vein and exposed to 20% phenol (wt/vol) in absolute ethanol for 5 minutes. In experiment 1, 32 male SHR were divided into two groups at 7 weeks of age and placed on either the basal or high NaCl diet. Two weeks later (9 weeks of age) each diet group was subdivided into bilateral renal denervated and sham-operated groups (n=8), and the initial renal denervation or sham operation was performed. All rats received a second operation 3 weeks later to prevent reinervation.

Food intake, water intake, and urine volume were measured for 4 consecutive days/wk while the animals were in individual metabolic cages to assess the effects of renal denervation or the diets on sodium and water balance. Seven weeks after initiation of the experiment, all rats were killed by decapitation without anesthesia. Trunk blood was collected in a heparinized tube at 4°C for determination of plasma creatinine and sodium concentrations. Plasma and urinary creatinine concentrations were measured spectrophotometrically at 520 nm using a CAP method (Stanbio Labs. Inc., San Antonio, Texas). Plasma and urinary sodium concentrations were measured by flame photometry (model 643, Instrumentation Laboratory Inc., Lexington, Massachusetts). Heart and kidneys were removed and weighed. Kidneys were frozen in liquid nitrogen and maintained at −80°C until subsequent assay.

To verify the effectiveness of the denervation, one kidney from each rat was used for the determination of renal catecholamine content by high-performance liquid chromatography with electrochemical detection after alumina extraction. The kidney was weighed and homogenized in 0.1N perchloric acid, and then centrifuged (15,000g) for 10 minutes at 4°C. The supernatants were extracted with activated alumina (Bioanalytical Systems Inc., West Lafayette, Indiana) containing internal standard (N-methyldopamine), and the catecholamines were eluted with 0.05N perchloric acid and filtered through 0.2 μm nylon filters by centrifugation.

Renal α2- and α2-adrenergic receptor binding was assessed in the opposite kidney using the α2-adrenergic receptor antagonist [3H]prazosin (PRA) (82.0 Ci/m mole) and the α2-adrenergic receptor agonist [3H]p-aminoclonidine (PAC) (42.0 Ci/m mole, New England Nuclear, Boston, Massachusetts). The method for radioligand binding was similar to that previously described by Sripanidkulchai et al. The kidneys were homogenized in 20 volumes of 50 mM Tris-HCl buffer (pH 7.6) and centrifuged at 50,000g for 15 minutes. The pellets were washed in the same buffer and the final pellets were resuspended in 50 mM Tris-HCl buffer containing 1.0 mM EDTA and 0.05% ascorbic acid ([3H]PRA experiments) or 10.0 mM MgCl2 ([3H]PAC experiments). In all assays, the final mixture (500 μl) contained 0.3–0.5 mg protein of the membrane suspension. After a 35-minute incubation at 25°C, the reaction was terminated by rapid filtration through Whatman GF/F filters and washing with 15 ml ice-cold Tris-HCl buffer (pH 7.6). The filters were placed in 10 ml scintillation cocktail (Budget Solve, Res. Prods. Intl. Corp., Mt. Prospect, Illinois), and after overnight stabilization in the dark, radioactivity was quantified by scintillation spectrometry at 47% efficiency. One and 10 nM concentrations of [3H]PAC were used to model the high and low affinity sites of α2-adrenergic receptors, respectively, and a 0.5 nM concentration of [3H]PRA was employed to detect α2-adrenergic receptor binding. For saturation analysis, 0.1–40 nM [3H]PAC and 0.05–5.0 nM [3H]PRA were used under standard assay conditions.

In experiment 2, 32 male SHR-S received renal denervation or sham operation at 6 weeks of age, 1 week before placement of half of each operated group (n=8) on the high NaCl diet. The denervation or sham operation was repeated 3 weeks after the first surgery (i.e., 9 weeks of age) to insure continued denervation. Throughout the study, the rats were maintained in metabolic cages and daily determination of sodium and water intake and excretion were calculated. After 5 weeks on these diets, while
under deep ether anesthesia, the right femoral arteries of all rats were cannulated with PE-10 tubing for subsequent measurement of mean arterial pressure and to facilitate blood withdrawal. One week after cannulation, in unanesthetized, resting rats, blood was collected in tubes containing 1.8 mg EGTA and 1.2 mg glutathione at 4°C, and plasma catecholamine concentrations were determined using the Cat-A-Kit radioenzymatic method (Amersham International plc, Chicago, Illinois). At the end of the experiment, all rats were decapitated without anesthesia. Trunk blood was collected in heparinized tubes for measurement of plasma sodium and creatinine concentrations. Heart and kidneys were removed and weighed. Kidneys were frozen in liquid nitrogen and kept at -80°C for determination of renal catecholamine content and renal concentration of α₁- and α₂-adrenergic receptors.

The results were expressed as mean±SEM and were tested by analysis of variance with appropriate post hoc analyses. All blood pressure measurements and biochemical analyses were conducted by investigators who were unaware of the group to which individual rats belonged.

Results

Experiment 1

After 2 weeks systolic blood pressure in SHR-S on the high NaCl diet was significantly higher than in SHR-S on the basal NaCl diet. The difference in blood pressure between groups continued to increase until approximately 4 weeks after the initiation of the diets, at which point it stabilized (Figure 1). Bilateral renal denervation delayed the rise of blood pressure in SHR-S on the high NaCl diet and prevented a significant rise of blood pressure in SHR-S on the basal NaCl diet, but it had no greater effect in SHR-S on high (compared with basal) NaCl diet. Further, the high NaCl diet increased blood pressure by approximately the same amount in the renal denervated and innervated SHR-S (Figure 1). There were no significant differences in the body weights of the four groups during the first 5 weeks of the experiment, but subsequently (at 12–14 weeks of age) the SHR-S on the high NaCl diet had lower body weights than the SHR-S on the basal NaCl diet (236±4, sham/high; 225±4, denervated/high; 248±4, sham/basal, and 255±5 g, denervated/basal).

Renal denervation did not affect food or water intake. The SHR-S on the high (compared with basal) NaCl diet drank significantly more water (93±3 compared with 30±1 ml/day). Denervated SHR-S on a basal NaCl diet excreted significantly more urinary sodium than the sham-operated SHR-S on the same diet, while denervated SHR-S on the high NaCl diet excreted approximately the same amount of sodium as sham-operated SHR-S on the high NaCl diet (Table 1).

The heart weight/body weight and total kidney weight/body weight ratios were significantly higher in the high (compared with basal) NaCl-fed SHR-S (Table 2) and denervation did not affect these ratios. Noradrenaline content in the denervated kidneys was less than 5% of that in sham-operated kidneys in SHR-S on either diet 2 weeks after the second operation (154±32, sham/basal; 4±2, denervated/basal; 123±24, sham/high; and 3±1 pg/mg denervated/high) indicating the effectiveness of the renal denervation. There was no significant difference in creatinine clearance between sham-operated and renal-denervated rats on either diet (0.63±0.06, sham/basal; 0.61±0.07, denervated/basal; 0.61±0.03, sham/high; and 0.64±0.03 ml/min/100 g body wt, denervated/high) suggesting that renal denervation and high NaCl diet did not affect the glomerular filtration rate. Neither the high NaCl diet nor surgery affected plasma sodium concentration.

The densities of high and low affinity renal α₁-adrenergic receptors (1 nM and 10 nM [³H]PAC binding, respectively) were increased in SHR-S on high NaCl (compared with basal) NaCl diet (Figure 2). In both diet groups, binding at the high and low

| TABLE 1. Percent Urinary Sodium Excretion Compared With Dietary Sodium Intake of NaCl-Sensitive Spontaneously Hypertensive Rats in Experiment 1 |
|---|---|---|---|---|---|
| Diet | Operation | Weeks after the first operation |
|---|---|---|---|---|
| Basal | Sham | 0 | 1 | 2 | 3 | 4 |
| Basal | Denervated | 80±4* | 80±5* | 91±6* | 85±3* |
| High | Sham | 80±6 | 77±3 | 87±7 | 86±6 | 77±5 |
| High | Denervated | 78±5 | 93±8 | 89±6 | 80±3 |

Values are mean±SEM.

*p<0.05 compared with the group on the same diet.
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Table 2. Heart Weight/Body Weight and Two Kidney Weight/Body Weight Ratios and Scatchard Analysis of 

<table>
<thead>
<tr>
<th>Diet</th>
<th>Operation</th>
<th>HW/BW (mg/g)</th>
<th>KW/BW (mg/g)</th>
<th>High affinity</th>
<th>Low affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Kd</td>
<td>Bmax</td>
</tr>
<tr>
<td>Basal</td>
<td>Sham</td>
<td>6.9±0.1</td>
<td>3.9±0.2</td>
<td>1.6</td>
<td>53</td>
</tr>
<tr>
<td>Basal</td>
<td>Denervated</td>
<td>6.7±0.1</td>
<td>3.6±0.1</td>
<td>1.7</td>
<td>74</td>
</tr>
<tr>
<td>High</td>
<td>Sham</td>
<td>8.4±0.3*</td>
<td>4.3±0.1*</td>
<td>1.5</td>
<td>71</td>
</tr>
<tr>
<td>High</td>
<td>Denervated</td>
<td>8.8±0.4*</td>
<td>4.3±0.3*</td>
<td>1.6</td>
<td>92</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Scatchard data represent results of two replication and are expressed as nanomoles and femtomoles per milligram protein for binding affinity ($K_d$) and receptor number ($B_{max}$), respectively. HW/BW, heart weight/body weight ratio; KW/BW, kidney weight/body weight ratio.

* $p<0.05$ compared with basal NaCl-fed, NaCl-sensitive spontaneously hypertensive rats undergoing the same operation.

 affinity sites was greater after renal denervation. The increase in binding attributable to the denervation was approximately the same in both groups (Figure 2). Scatchard analysis of [3H]PAC binding demonstrated that the alterations in binding due to NaCl loading and renal denervation were the result of changes in receptor number ($B_{max}$) but not binding affinity ($K_d$) (Table 2). In contrast, $\alpha_1$-adrenergic receptor ([3H]PRA) binding was not affected by either diet or by renal denervation (Figure 2). Scatchard analysis revealed that neither the affinity nor the number of $\alpha_1$-adrenergic receptors was altered in these four groups of SHR-S.

Experiment 2

In the second experiment, renal denervation was performed at 6 weeks of age, 1 week before initiation of the high NaCl diet. One week after the operation, systolic blood pressure of the denervated rats was significantly lower than that of the sham-operated rats (135±4 vs. 148±4 mm Hg, $p<0.05$). The systolic blood pressure of sham-operated SHR-S on the high NaCl diet was elevated significantly above that of the renal-denervated SHR-S on the high NaCl diet after 1 week on the high NaCl diet. From 2 weeks after the initiation of the diets to the end of the experiment, the systolic blood pressure of denervated rats in both diet groups was significantly below that of sham-operated rats on the same diet (Figure 3), but denervation effected a similar, absolute decrease in systolic blood pressure in SHR-S on basal and high NaCl diets. Direct mean arterial pressure measurements taken at the end of the study correlated significantly ($p<0.001$) with the indirect pressure measurements.

Weight gain was similar in the four groups of rats except during the last 2 weeks of the experiment (11 and 12 weeks of age), at which time the sham-operated group on the basal NaCl diet was significantly heavier than the other three groups (254±4, sham/basal; 239±4, denervated/basal; 238±7, sham/high, and 237±6 g, denervated/high).

The high NaCl diet increased water intake and urinary sodium and volume excretion in both denervated and sham-operated SHR-S, but renal denervation...
vation did not affect food or water intake of SHR-S on either diet. Urinary sodium excretion also increased significantly in the denervated (compared with sham-operated) rats receiving basal NaCl diets, but not in denervated SHR-S on the high NaCl diet. At 12 weeks of age (after 5 weeks on the high NaCl diet), the heart weight/body weight and kidney weight/body weight ratios of SHR-S (both sham-operated and denervated groups) on high NaCl diet were greater than those of basal NaCl-fed SHR-S. The ratios of heart weight/body weight and kidney weight/body weight were nearly identical to those shown in Table 2 for experiment 1.

Plasma noradrenaline (181±7, sham/basal; 229±24, denervated/basal; 244±24, sham/high; and 252±30 pg/ml, denervated/high) and adrenaline (38±5, sham/basal; 47±13, denervated/basal; 92±23, sham/high; and 74±26 pg/ml, denervated/high) concentrations were greater in rats on the high (compared with basal) NaCl diet, and renal denervation did not decrease the concentration of either catecholamine. When tested 3 weeks after the second denervation, biochemical analysis demonstrated that the noradrenaline was still reduced by more than 85% in both basal and high NaCl-fed denervated SHR-S (333±69, sham/high; 50±15, denervated/high; 206±41, sham/basal, and 26±7 pg/mg tissue, denervated/basal) 3 weeks after the second denervation, and plasma sodium concentration was not changed by either diet or surgery.

Renal α2-adrenergic receptors were increased significantly by both high NaCl diet and renal denervation (Figure 4). As in experiment 1, Scatchard analysis revealed that $B_{\text{max}}$ was increased, but $K_d$ remained unchanged after both interventions. The density and affinity of renal α2-adrenergic receptors were not affected by either diet or renal denervation.

**Discussion**

Recent data from our laboratory suggest that dietary NaCl supplementation causes a centrally mediated sympathoinhibitory defect that appears in association with an increase in blood pressure in SHR-S. After 2 weeks of feeding a high (compared with basal) NaCl diet, the turnover of noradrenaline is dramatically reduced in the anterior hypothalamic region of SHR-S but not in NaCl-resistant SHR (SHR-R) or normotensive WKY rats, which are also NaCl insensitive. The decrease in noradrenaline release is associated with an upregulation of α2-adrenergic receptors in the anterior hypothalamic area and increased responsiveness of neurons in this region to α2-adrenergic receptor agonist stimulation. This dietary NaCl-induced defect in noradrenaline release in the anterior hypothalamic area of SHR-S likely results in a lack of sympathoinhibition and a secondary rise in blood pressure. The present study tests the hypothesis that increased efferent renal nerve activity contributes to the hypertensive effects of the high NaCl diet in this model.

Previous data from our laboratory demonstrate the importance of the efferent renal nerves in the development of both genetic (SHR) and NaCl-induced (DOCA-NaCl) models of hypertension. In these two models, renal denervation causes an increase in sodium excretion and a concomitant reduction in hypertension, suggesting that increased renal nerve activity, in association with an increase in sodium retention, contributes to the development of these forms of hypertension. Further, Koepke and DiBona have demonstrated in SHR that high dietary NaCl exaggerates renal nerve responses to acute air puff stress, an effect that would be expected to increase sodium retention and thereby raise blood pressure. In contrast, a recent study from this laboratory demonstrates that in the Dahl salt-sensitive (DS) model, the renal nerves do not contribute importantly to the development of hypertension: renal denervation failed to attenuate the development of hypertension and to increase urinary sodium excretion. Thus, although increased total peripheral sympathetic nervous system activity plays an important role in the development of the NaCl-induced rise in blood pressure in DS rats, our results suggest that neurally mediated renal sodium retention does not.

The results of the current study suggest a similar dissociation between increased total peripheral sympathetic nervous system activity and functionally significant, increased efferent renal nerve activity in the dietary NaCl-loaded SHR-S. Although renal denervation attenuated the development of hypertension in this model, it had no greater effect in the high NaCl diet than basal diet SHR-S. The high NaCl diet increased blood pressure by the same amount in the innervated and denervated SHR-S. This suggests that the NaCl-induced exacerbation of hypertension is not dependent on renal nerve activity.

In SHR-S on the basal NaCl diet, renal denervation was associated with a significant increase in sodium excretion, thus confirming the results of our earlier study. In contrast, no increase in sodium...
excretion was detected in renal denervated SHR-S maintained on the high NaCl diet. This may be related to the difficulty of detecting a small (0.5 meq sodium/day in the basal NaCl diet group), but biologically important, renal nerve-mediated component of renal sodium handling in the presence of a greatly accelerated (>20 meq sodium/day) natriuresis. It should be noted that renal denervation was as complete in the present study as in past experiments, resulting in a greater than 85% depletion of noradrenaline in denervated (compared with sham operated) kidneys. The effectiveness of the denervation was confirmed by concurrent immunohistochemical studies, which demonstrated the absence of tyrosine hydroxylase (the rate limiting enzyme in noradrenaline production) in the kidneys 2 weeks after denervation (unpublished observation from our laboratory). Also, in concurrent studies we demonstrated that denervation eliminated retrograde, neuronal labeling after injections of tracers into the renal nerve distal to the lesion.

Receptor supersensitivity could contribute to the present denervation results. Kline and Mercer demonstrated that within 96 hours after renal denervation, stimulation of the kidney with noradrenaline causes a significantly greater than normal pressor response. The high NaCl diet increases circulating noradrenaline in SHR-S, and it is possible that supersensitive receptors in the denervated kidney would be more responsive than normal to stimulation by circulating noradrenaline. In this regard it should be noted that α2-adrenergic receptors do not show long-term upregulation in the SHR-S in response to denervation. The α2-adrenergic receptor is the primary receptor involved in vasoconstriction of the renal vascular bed, and thus it seems less likely that denervation supersensitivity would mask the renal nerve contribution to NaCl-exacerbated hypertension in this model.

In the present study, renal α2-adrenergic receptors increased in number after renal denervation in SHR-S on both basal and high NaCl diets, but renal α1-adrenergic receptor binding was not altered by renal denervation. These results suggest that the loss of sympathetic nerve terminals in the kidney is compensated by a long lasting increase in α2- (but not α1-) adrenergic receptors. The absence of α2-adrenergic receptor upregulation in renal-denervated SHR-S was unexpected, since reports by Woodcock et al and Yamada et al demonstrated renal α1-adrenergic receptor number is increased 1 week after renal denervation. But the denervation-induced upregulation of renal α1-adrenergic receptors appears to be only a short-term response, since 3 to 6 weeks (vide supra) after denervation α1-adrenergic receptor number was similar in denervated and control rats. Further, small changes in α1-adrenergic receptor number may be difficult to detect, since there are fewer α1- than α2-adrenergic receptors in the rat kidney. In accordance with the present results, studies of Yamada et al demonstrated that the percent increase of renal α2-adrenergic receptors is greater than that of α1-adrenergic receptors after renal denervation. The upregulation of renal α2-adrenergic receptors can be detected from 4 days to 6 weeks (present results) after denervation.

Early studies suggest that the renal α2-adrenergic receptors are localized primarily on the proximal tubule and mediate sodium reabsorption, but more recent studies in the rat suggest that the α2-adrenergic receptor in the kidney is not involved in sodium reabsorption. Other studies indicate that α2-adrenergic receptors reside in the medulla, where they likely are associated with the collecting ducts. The potential physiological importance of this finding is suggested by experiments demonstrating that renal α2-adrenergic receptors are important in mediating sodium and water excretion at the collecting duct by antagonizing the effect of vasopressin.

The present results, together with past findings, suggest that the renal α2-adrenergic receptors do not play an important role in the initiation of hypertension. First, both cortical and medullary α2-adrenergic receptors are increased in SHR-S in response to dietary NaCl supplementation, indicating that the sodium-induced changes in adrenergic receptor number are not specific to α2-adrenergic receptor-mediated reabsorption of sodium at the proximal tubule. Second, the change in α2-adrenergic receptor number in the kidney is not present during the early developmental phase (1 week after loading) of NaCl-exacerbated hypertension in SHR-S (unpublished data). Third, a recent study by Parini et al suggests that modifications in renal receptors are not responsible for the impairment of sodium reabsorption in the Milan hypertensive rat but may facilitate the normalization of renal function in adult rats. In SHR-S and DS rats on high NaCl diets and in DOCA-NaCl rats, renal α2-adrenergic receptor upregulation occurs, suggesting that some common factor associated with elevated blood pressure effects these increases. Further, the renal α2-adrenergic receptor changes do not occur early in the developmental phase of these models. Together with the pharmacological studies noted above, these findings suggest that the increase in α2-adrenergic receptors are compensatory to the hypertensive derangement.

In summary, the results of the present study demonstrate that destruction of the renal nerves prevents the full development of hypertension in SHR-S maintained on a basal NaCl diet and attenuates the development of hypertension in SHR-S on a high NaCl diet. Second, the data demonstrate that a high NaCl diet can exacerbate hypertension in the SHR-S independent of the renal nerves, and third, the results indicate that renal denervation does not lower plasma noradrenaline levels in either the basal or the high NaCl diet group, indicating that the hypotensive effect of renal denervation in SHR-
S is not dependent on a reduction in peripheral sympathetic nervous system activity. Future studies should focus on circulating hormonal factors, on endogenous renal abnormalities that limit the NaCl handling ability of the SHR-S kidney, and on factors, including the renal nerves, that may facilitate renal function in NaCl-resistant rats.

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