Impaired Renal Vascular Reactivity in Prehypertensive Dahl Salt-Sensitive Rats

Shlomoh Simchon, William M. Manger, Guo-Shan Shi, and Jeffrey Brensiver

We have previously shown that renal vascular resistance is less in Dahl salt-sensitive rats than salt-resistant rats fed 1% NaCl diets; however, renal vascular resistance increases before nonrenal vascular resistance as salt-sensitive rats develop hypertension when fed 8% NaCl diets. When salt-resistant rats are given 8% NaCl diets, renal vascular resistance decreases. The current study reports effects of atrial natriuretic peptide, nitroprusside, norepinephrine, angiotensin II, and endothelin-1 on renal and nonrenal vascular resistance in prehypertensive salt-sensitive and salt-resistant rats given 1% NaCl diets; doses used did not affect blood pressure. Resistance of nonrenal vessels in salt-sensitive and salt-resistant rats responded similarly to dilators or constrictors. However, atrial natriuretic peptide and nitroprusside decreased renal vascular resistance of salt-resistant rats (by 65%, p<0.01) but not that of salt-sensitive rats. Norepinephrine, angiotensin II, and endothelin-1 increased renal vascular resistance in salt-sensitive rats by 126%, 135%, and 135%, respectively (p<0.01); norepinephrine and angiotensin II did not change renal vascular resistance of salt-resistant rats, but endothelin-1 decreased renal vascular resistance in salt-resistant rats by 30% (p<0.01). Reactivity of nonrenal blood vessels in prehypertensive salt-sensitive and salt-resistant rats was similar when infused with dilators or constrictors in doses used. By contrast, renal vessels of salt-sensitive rats did not dilate in response to atrial natriuretic peptide and nitroprusside but were hypersensitive to norepinephrine and angiotensin II. Endothelin-1 caused renal vasoconstriction in salt-sensitive rats and renal vasodilation in salt-resistant rats. Inappropriate renal vascular reactivity in prehypertensive salt-sensitive rats may play an important role in salt-induced hypertension. (Hypertension 1992;20:524–532)

Key Words: cardiac output • microspheres • renal circulation • vascular resistance • hypertension, sodium-dependent • rats, inbred strains

There is compelling evidence indicating an important role for the kidney and salt (NaCl) in the genesis of hypertension1; however, the precise mechanism whereby salt elevates blood pressure remains unknown. The strain of salt-sensitive (DS) and salt-resistant (DR) rats developed by Dahl and coworkers2 has been especially useful as an animal model for studying experimental hypertension. Some evidence implicates humoral factors,3,4 neurogenic mechanisms,5 and a deficient natriuretic capacity of the kidney6–8 as possible causes of salt-induced hypertension in DS rats. Studies by Dahl et al9 demonstrated that transplanting kidneys from DR rats into DS rats prevented salt-induced hypertension, whereas transplanting kidneys from DS rats into DR rats permitted salt-induced hypertension. From these results, they concluded that genetically determined characteristics of DS kidneys were responsible for salt sensitivity and the development of hypertension. However, Morgan et al10 recently reported that, in addition to renal factors, extrarenal factors contribute to salt-induced hypertension.

Several anatomical differences between DS and DR kidneys have been reported. Azar et al11 demonstrated fewer glomeruli and fewer functioning nephrons in DS than DR kidneys. Whether a diminished number of glomeruli and nephrons or a deficiency of a putative antihypertensive lipid elaborated by renomedullary interstitial cells12 play a role in the development of salt-induced hypertension is unclear.

Tobian et al,8 Roman,6 and Roman and Osborn7 demonstrated a reduction in the natriuretic capacity of DS kidneys. They concluded that development of hypertension in DS rats on a high salt diet was a compensatory response that prevented salt and water retention. Studies by Hirata et al13 on the isolated perfused kidney revealed a lower renal papillary plasma flow in DS than in DR kidneys; however, recent in vivo studies did not confirm these findings.14 Hirata et al13 further demonstrated that kidneys of DS rats were hyporesponsive to atrial natriuretic peptide (ANP) extracted from atria of Sprague-Dawley rats when compared with the response in DR rats. Using synthetic ANP, we also demonstrated that DS kidneys were hyporesponsive to this peptide, whereas it caused a pronounced natriuresis and diuresis in DR rats.15

We previously suggested that hypertension that developed in DS rats in response to a high salt diet (8%...
NaCl) for 4 weeks resulted, at least partly, from an inability of the kidney to vasodilate and cause natriuresis. Thus, abnormal renal hemodynamics may play an important role in initiating hypertension in DS rats on a high salt diet. However, Green et al. demonstrated that hypertension is related to volume expansion and not dependent on salt retention. According to Guyton, in the presence of an increased cardiac output (CO) and augmented tissue blood flow, total peripheral resistance (TPR) increases significantly with "long term autoregulation" (i.e., vasoconstrictor regulation of tissue perfusion) and CO returns to normal; elevated peripheral resistance then becomes responsible for the hypertension. In our studies, an expanded blood volume and an increased CO initiated hypertension, whereas after 8 weeks an increased TPR sustained the hypertension. We also demonstrated a second mechanism for salt-induced hypertension in DS rats. This second mechanism involved an increased TPR after ingesting a 1% NaCl diet for 46 weeks; CO decreased and blood volume was unchanged.

In the current study we report the effects of ANP, nitroprusside, norepinephrine, angiotensin II (Ang II), and endothelin-1 (ET-1) infusions on renal vascular resistance (RVR) and non-RVR in prehypertensive DS and DR rats fed a 1% salt diet; doses were used that did not affect blood pressure. The effects on hemodynamics of increasing the nitroprusside dose to reduce blood pressure to 50% of control was also studied to observe whether large doses of this agent significantly augmented renal and nonrenal vascular dilation in DS and DR rats.

Methods

Procedures

Experiments are reported on 25 male DR and 25 DS rats (Brookhaven National Laboratory, Upton, N.Y. and Harlan Sprague Dawley Inc., Indianapolis, Ind.) that had been fed normal (1% NaCl) Purina rat chow (Purina Mills Co., Richmond, Ind.) from weaning. Rats were subjected to one of the following protocols.

Protocol A: Effect of atrial natriuretic peptide infusion. Synthetic rat ANP (28 amino acids, Sigma Chemical Co., St. Louis, Mo.) was dissolved in 5% dextrose in water and infused intravenously at two doses (1.4 and 2.7 ng/min or 0.004±0.0003 and 0.008±0.0006 ng·min⁻¹·g body weight for 15 minutes each, doses that did not affect blood pressure) into prehypertensive 8-week-old rats (n=5 for DR and 5 for DS rats) that had been maintained since weaning on a 1% NaCl diet. A recovery period of 10 minutes was allowed between the two infusion doses.

Protocol B: Effect of nitroprusside infusion. Sodium nitroprusside, USP (Nitropress, Abbott Laboratories, North Chicago, Ill.) was dissolved in 5% dextrose in water (and protected from light by aluminum foil wrapping) and infused intravenously at two doses. The first dose (125 ng/min or 0.35±0.02 ng·min⁻¹·g body weight for 15 minutes) did not significantly affect blood pressure; the second infusion rate was adjusted to decrease arterial pressure by 50% in prehypertensive 8-week-old rats (n=5 for DR and 5 for DS rats) that had been maintained since weaning on a 1% NaCl diet. A recovery period of 10 minutes was allowed between the two infusion doses.

Protocol C: Effect of norepinephrine infusion. Norepinephrine (Levophed bitartrate, Winthrop Pharmaceuticals, New York) was dissolved in 5% dextrose in water and infused intravenously at two doses (2.7 and 5.4 ng/min or 0.0075±0.0002 and 0.015±0.004 ng·min⁻¹·g body weight for 15 minutes each, doses that did not significantly affect blood pressure) into prehypertensive 8-week-old rats (n=5 for DR and 5 for DS rats) that had been maintained since weaning on a 1% NaCl diet. A recovery period of 10 minutes was allowed between the two infusion doses.

Protocol D: Effect of angiotensin II infusion. Ang II (acetate salt, Sigma Chemical Co., St. Louis, Mo.) was dissolved first in preheated 10% bovine serum albumin and then reconstituted in 5% dextrose in water and infused intravenously at two doses (1.4 and 2.7 ng/min or 0.004±0.0003 and 0.008±0.0006 ng·min⁻¹·g body weight for 15 minutes each, doses that did not affect blood pressure) into prehypertensive 8-week-old rats (n=5 for DR and 5 for DS rats) that had been maintained since weaning on a 1% NaCl diet. A recovery period of 10 minutes was allowed between the two infusion doses.

Protocol E: Effect of endothelin-1 infusion. ET-1 (Peninsula Laboratories, Inc., Belmont, Calif.) was dissolved in 5% dextrose in water and infused intravenously at two doses (2.6 and 5.0 ng/min or 0.007±0.0004 and 0.014±0.001 ng·min⁻¹·g body weight for 15 minutes each, doses that did not affect blood pressure) into prehypertensive 6-week-old rats (n=5 for DR and 5 for DS rats) that had been maintained since weaning on a 1% NaCl diet. A recovery period of 10 minutes was allowed between the two infusion doses.

Surgical Procedure

After anesthesia with sodium pentobarbital (35 mg/kg i.p.), a polyethylene catheter (PE-290) was inserted through the abdominal aorta via a femoral artery for blood withdrawal and recording of arterial pressure (volume removed during blood sampling was simultaneously replaced by intravenous infusion of an equal volume of donor blood). A third catheter (PE-50) was inserted in the jugular vein for intravenous infusions. A fourth catheter was advanced via the carotid artery into the left ventricle for injection of microspheres; the position of the catheter tip was confirmed by pressure tracing. Cardiovascular pressures were monitored using Statham transducers and a polygraph recorder (model 7, Grass Instrument Co., Quincy, Mass.). The rats were used according to National Institutes of Health and New York University Medical Center guidelines for animal care.

Methods

Hemodynamic parameters. CO and blood flow distribution were determined by a microsphere method (previously validated in our laboratory by comparison with electromagnetic flowmeter and xenon-133 washout technique using 15.0±1.0 μm diameter microspheres (New England Nuclear Corp., Boston, Mass.) injected into the left ventricle in about 45 seconds. Three measurements were made using latex microspheres labeled with radionuclides cobalt-57, tin-113,
and scandium-46 (Figure 1). An injection of microspheres labeled with one isotope was given before the first infusion for control blood flow measurements. A second injection of microspheres labeled with another isotope was given 15 minutes after the first infusion was started, and the third injection of microspheres labeled with still another isotope was given 15 minutes after the second infusion was started for blood flow measurements. The use of microspheres labeled with three different radionuclides permits determination of blood flow at three different time periods in the same animal. (We have found that repeated injection of different microspheres into the rat over time does not significantly alter renal blood flow \[\text{RBF}\] \[625 \pm 16.8, 619 \pm 23.6, \text{and } 621 \pm 17.7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1}\] kidney weight, respectively, after injecting different microspheres at intervals of 30 minutes, \(p > 0.5\).) Reference blood samples were withdrawn from the abdominal aorta at a rate of 0.8 ml/min for 2 minutes (total of 1.6 ml blood; withdrawal of the blood was started 10–15 seconds before injection of microspheres, and blood was simultaneously replaced by infusion of donor blood). At the end of the experiment, rats were killed by injecting a saturated KCl solution into the left ventricle, and blood was withdrawn 10 seconds before injection of microspheres into the rat over time does not significantly change occurred in blood pressure (Table 3 and Figure 2); RVR decreased 30% in DR rats \((p < 0.01)\) but remained unchanged in DS rats (Figure 3). At a higher dose of nitroprusside, when blood pressure decreased by 50% (due to a diminished CO and TPR, Table 3), non-RVR decreased 30% in DR and DS rats \((p < 0.01)\); blood pressure did not change significantly (Table 2 and Figure 2). There was no difference in the response between DR and DS rats. ANP infusion at a subdepressor dose caused an increase in CO in DS and DR rats \((p < 0.01)\) that was accompanied by a significant decrease in TPR in DR and DS rats \((p < 0.01)\); blood pressure did not change significantly (Table 2 and Figure 2). There was no difference in the response between DR and DS rats.

Nitroprusside infusion at a subdepressor dose caused increases in CO and decreases in TPR and non-RVR that were similar in DS and DR rats, but no significant change occurred in blood pressure (Table 3 and Figure 2); RVR decreased 30% in DR rats \((p < 0.01)\) but remained unchanged in DS rats (Figure 3). At a higher dose of nitroprusside, when blood pressure decreased by 50% (due to a diminished CO and TPR, Table 3), non-RVR decreased 30% in DR and DS rats \((p < 0.01)\); RVR decreased 50% in DR \((p < 0.01)\) but again remained unchanged in DS rats (Figure 3).

Norepinephrine infusions at two suppressor doses caused no significant changes in CO, TPR, blood pressure, and non-RVR in DS and DR rats (Table 4 and Figure 4). At the lower dosage RVR increased 40% in DS \((p < 0.01)\) but remained unchanged in DR rats; at the higher dosage RVR increased 126% in DS \((p < 0.01)\) but remained unchanged in DR rats (Figure 4).

### Results

Control values for all 25 DS and 25 DR rats before infusions are summarized in Table 1. RVR in DS rats was lower than in DR rats \((p < 0.01)\); however, control blood pressure, CO, and TPR values in DS and DR rats were similar.

\[
\text{Percent change} = \frac{\text{experimental results} - \text{control value}}{\text{control value}} \times 100
\]

Significance of changes was statistically evaluated by analysis of variance, followed by Student-Newman-Keuls test for multiple comparison (minimal level for statistical significance is \(p < 0.05\)).

### Table 1. Systemic and Renal Hemodynamic Control Data of 8-Week-Old Prehypertensive Rats Before Infusion With Vasoactive Substances

<table>
<thead>
<tr>
<th>Rat group</th>
<th>(n)</th>
<th>MABP (mm Hg)</th>
<th>Body wt (g)</th>
<th>CO (ml/min)</th>
<th>TPR (mm Hg (\cdot) (\text{ml}^{-1} \cdot \text{sec}^{-1}))</th>
<th>Non-RVR (mm Hg (\cdot) (\text{ml}^{-1} \cdot \text{sec}^{-1}))</th>
<th>RBF (ml (\cdot) 100 g(^{-1}))</th>
<th>RVR (mm Hg (\cdot) (\text{min}^{-1} \cdot) (100 \text{ g}^{-1}))</th>
<th>Kidney wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td>25</td>
<td>103 ± 7</td>
<td>344 ± 17.9</td>
<td>123 ± 7.5</td>
<td>50.1 ± 4.5</td>
<td>58.2 ± 4.2</td>
<td>524 ± 52</td>
<td>11.8 ± 1.8</td>
<td>3.3 ± 0.2</td>
</tr>
<tr>
<td>DS</td>
<td>25</td>
<td>104 ± 6</td>
<td>360 ± 15.2</td>
<td>130 ± 8.6</td>
<td>47.8 ± 5.2</td>
<td>58.2 ± 5.5</td>
<td>734 ± 62*</td>
<td>8.5 ± 1.7*</td>
<td>3.1 ± 0.3</td>
</tr>
</tbody>
</table>

MABP, mean arterial blood pressure; CO, cardiac output; TPR, total peripheral resistance; Non-RVR, nonrenal vascular resistance; RBF, renal blood flow; RVR, renal vascular resistance; DR, Dahl salt-resistant rats; DS, Dahl salt-sensitive rats. Values given are mean ± SD.

*Control DS rat measurements statistically different from control measurements in DR rats \((p < 0.01)\).
Table 2. Systemic and Renal Hemodynamic Data After Infusion With Atrial Natriuretic Peptide

<table>
<thead>
<tr>
<th>Rat group</th>
<th>MABP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>TPR (mm Hg·ml⁻¹·sec⁻¹)</th>
<th>Non-RVR (mm Hg·ml⁻¹·sec⁻¹·100 g⁻¹)</th>
<th>RBF (ml·min⁻¹·100 g⁻¹)</th>
<th>RVR (mm Hg·ml⁻¹·sec⁻¹·100 g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td>110±12</td>
<td>121±3</td>
<td>54.6±3</td>
<td>62.2±3</td>
<td>452±24</td>
<td>14.7±1.9</td>
</tr>
<tr>
<td>Control</td>
<td>90±3</td>
<td>165±12*</td>
<td>32.7±2*</td>
<td>41.4±2*</td>
<td>1,050±15*</td>
<td>5.1±0.3*</td>
</tr>
<tr>
<td>ANP</td>
<td>108±12</td>
<td>124±3</td>
<td>51.8±2</td>
<td>62.0±3</td>
<td>671±49†</td>
<td>9.6±1.6†</td>
</tr>
<tr>
<td>DS</td>
<td>100±6</td>
<td>170±15*</td>
<td>35.3±1*</td>
<td>40.2±2*</td>
<td>630±28</td>
<td>9.5±0.4</td>
</tr>
</tbody>
</table>

MABP, mean arterial blood pressure; CO, cardiac output; TPR, total peripheral resistance; Non-RVR, nonrenal vascular resistance; RBF, renal blood flow; RVR, renal vascular resistance; DR, Dahl salt-resistant rats; ANP, atrial natriuretic peptide; DS, Dahl salt-sensitive rats. Mean body weight DR rat, 352±7 g; DS rat, 381±6 g. Mean kidney weight DR rat, 3.29±0.1 g; DS rat, 3.05±0.2 g.

At the lower dosage RVR increased 20% in DS (p<0.01) but remained unchanged in DR rats; at the higher dosage RVR increased 135% in DS (p<0.01) but remained unchanged in DR rats (Figure 4).

ET-1 infusions at two subpressor doses caused increases in CO and decreases in TPR and non-RVR that were similar in DS and DR rats, but no significant change occurred in blood pressure (Table 6 and Figure 5). At the lower dosage, RVR decreased 24% in DR rats (p<0.01) but increased 36% in DS rats (p<0.01); at the higher dosage, RVR decreased 30% in DR rats (p<0.01) but increased 135% in DS rats (p<0.01, Figure 5).

**Discussion**

The objective of the present study was to determine whether renal vascular reactivity differed between prehypertensive DS and DR rats. Conceivably, an abnormality in renal vascular reactivity in DS rats might impair natriuresis and cause salt-induced hypertension. We...
RBF, renal blood flow; RVR, renal vascular resistance; DR, Dahl salt-resistant rats; NE, norepinephrine; DS, Dahl salt-sensitive rats. Mean body weight DR rat, 374±16 g; DS rat, 359±21 g. Mean kidney weight DR rat, 3.31 ±0.2 g; DS rat, 3.07±0.3 g.

**TABLE 4. Systemic and Renal Hemodynamic Data After Infusion With Norepinephrine**

<table>
<thead>
<tr>
<th>Rat group</th>
<th>MABP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>TPR (mm Hg·ml⁻¹·sec⁻¹)</th>
<th>Non-RVR (mm Hg·ml⁻¹·sec⁻¹)</th>
<th>RBF (ml·min⁻¹·100 g⁻¹)</th>
<th>RVR (mm Hg·ml⁻¹·sec⁻¹·100 g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>99±2</td>
<td>142±26</td>
<td>41.8±7</td>
<td>48.0±9</td>
<td>540±59</td>
<td>11.0±1.4</td>
</tr>
<tr>
<td>NP low dose</td>
<td>99±2</td>
<td>171±15</td>
<td>34.7±2</td>
<td>40.8±3</td>
<td>751±63*</td>
<td>7.9±0.7*</td>
</tr>
<tr>
<td>NP high dose</td>
<td>52±4*</td>
<td>115±9*</td>
<td>27.1±1*</td>
<td>32.8±3*</td>
<td>599±49</td>
<td>5.2±0.4*</td>
</tr>
<tr>
<td>DS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>100±10</td>
<td>155±15</td>
<td>38.7±6</td>
<td>45.5±9</td>
<td>710±73†</td>
<td>8.5±1.4†</td>
</tr>
<tr>
<td>NP low dose</td>
<td>99±3</td>
<td>174±16</td>
<td>34.1±3</td>
<td>39.0±2</td>
<td>665±52</td>
<td>8.9±0.6</td>
</tr>
<tr>
<td>NP high dose</td>
<td>50±3*</td>
<td>110±8*</td>
<td>27.2±1*</td>
<td>30.5±1*</td>
<td>351±29*</td>
<td>8.6±0.7</td>
</tr>
</tbody>
</table>

*Statistically different from control measurements (p<0.01).
†Control DS rat measurements statistically different from control measurements in DR rats (p<0.01).

Elected to infuse vasodilators (ANP and nitroprusside) and vasoconstrictors (norepinephrine, Ang II, and ET-1) in concentrations that would not significantly alter blood pressure to assess renal vascular reactivity to these agents without changes that might result from altering systemic pressure. Nitroprusside was also infused in a concentration that reduced mean arterial pressure by 50% to observe the effect of a higher concentration of this agent on renal and nonrenal vascular reactivity.

We have previously noted that conscious prehypertensive DS rats tended to have a lower baseline RVR than DR rats given a 1% NaCl diet. It is unclear why the RVR was significantly less in DS rats before infusion with vasoactive substances (Table 1). Fink and coworkers studied RVR and reactivity in autoperfused kidneys of anesthetized female DS and DR rats. Particularly noteworthy was their observation that RVR was also significantly lower in DS than DR rats on a "normal" (0.4% NaCl) salt diet; this agrees with our findings. Roman, Roman and Kaldunski, and Grossman et al using a flowmeter on the renal artery, reported baseline RBF and RVR to be similar in normotensive anesthetized DR and DS rats given low (0.3 or 0.1% NaCl) salt diets. Why our results and those of Fink et al differed from those of Roman and Grossman et al is unclear, but the lower salt diets that they used may have been responsible for differences.

Our results indicate that nonrenal blood vessels behave similarly in prehypertensive DS and DR rats; however, the renal vasculature responds differently. ANP and nitroprusside dilate the renal vasculature of DR rats but not that of DS rats. In the dosage used, norepinephrine and Ang II had no effect on renal vasculature of DR rats but constricted renal vasculature of DS rats. ET-1 caused renal vasodilation in DR rats but renal vasoconstriction in DS rats. These data indicate that renal vasculature of DS rats is hyporesponsive to the dilators and is hyperresponsive to the constrictors. The abnormal renal vascular response in DS rats to a variety of vasoactive agents suggests the possibility of an inherited defect in renal smooth muscle excitation-contraction coupling rather than multiple receptor defects that would be necessary to explain the abnormal responses to all agents tested. It appears that the prehypertensive DS renal vasculature might be nearly maximally dilated on a 1% NaCl diet, since it was unable to further dilate when ANP or nitroprusside was infused. However, Fink et al reported that intraarterial acetylcholine caused some additional renal vascular dilation in DS rats on a 0.4% NaCl diet.

**TABLE 4. Systemic and Renal Hemodynamic Data After Infusion With Norepinephrine**

<table>
<thead>
<tr>
<th>Rat group</th>
<th>MABP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>TPR (mm Hg·ml⁻¹·sec⁻¹)</th>
<th>Non-RVR (mm Hg·ml⁻¹·sec⁻¹)</th>
<th>RBF (ml·min⁻¹·100 g⁻¹)</th>
<th>RVR (mm Hg·ml⁻¹·sec⁻¹·100 g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>103±4</td>
<td>126±6</td>
<td>49.1±4</td>
<td>57.1±6</td>
<td>531±34</td>
<td>11.6±1.9</td>
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<tr>
<td>NE low dose</td>
<td>104±7</td>
<td>125±10</td>
<td>49.9±2</td>
<td>59.1±4</td>
<td>585±41</td>
<td>10.7±0.6</td>
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<tr>
<td>NE high dose</td>
<td>105±6</td>
<td>129±11</td>
<td>48.8±2</td>
<td>56.6±3</td>
<td>550±49</td>
<td>11.5±0.8</td>
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<td>DS</td>
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<td></td>
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<tr>
<td>Control</td>
<td>105±3</td>
<td>127±7</td>
<td>49.6±3</td>
<td>60.0±3</td>
<td>717±83*</td>
<td>8.8±3.3*</td>
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<tr>
<td>NE low dose</td>
<td>105±6</td>
<td>128±9</td>
<td>49.2±1</td>
<td>56.1±4</td>
<td>510±44†</td>
<td>12.4±0.9†</td>
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<tr>
<td>NE high dose</td>
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<td>128±9</td>
<td>49.2±1</td>
<td>53.4±4</td>
<td>330±26†</td>
<td>19.1±1.4†</td>
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MABP, mean arterial blood pressure; CO, cardiac output; TPR, total peripheral resistance; Non-RVR, nonrenal vascular resistance; RBF, renal blood flow; RVR, renal vascular resistance; DR, Dahl salt-resistant rats; NE, norepinephrine; DS, Dahl salt-sensitive rats. Mean body weight DR rat, 374±16 g; DS rat, 359±21 g. Mean kidney weight DR rat, 3.31±0.2 g; DS rat, 3.07±0.3 g.

*Statistically different from control measurements (p<0.01).
The renal vasculature is regulated by many neurohumoral factors. Vascular endothelial cells release endothelium-derived relaxing factor (EDRF) and endothelium-derived constricting factor that can play a significant role in the regulatory mechanism of blood pressure and vascular function. Cyclic guanosine 3',5' monophosphate (cGMP), which is produced by activation of guanylate cyclase, is one of the mediators of vascular relaxation. Guanylate cyclase, the enzyme that produces cGMP, exists in at least two different molecular forms: one form is a soluble heme-containing enzyme consisting of two subunits, called "soluble guanylate cyclase"; the other form is a nonheme-containing transmembrane protein having a single subunit, called "particulate guanylate cyclase." The membrane form of guanylate cyclase is activated by ANP that binds to specific receptors of cell membranes. On the other hand, cytoplasmic soluble guanylate cyclase is activated by nitric oxide, which is produced by a variety of agents including nitrovasodilators such as nitroprusside. Nitric oxide was recently discovered to occur endogenously as one of the EDRFs.

**TABLE 5. Systemic and Renal Hemodynamic Data After Infusion With Angiotensin II**

<table>
<thead>
<tr>
<th>Group</th>
<th>Non-RVR</th>
<th>RBF RVR</th>
<th>MABP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>TPR (mm Hg·ml⁻¹·sec⁻¹)</th>
<th>Non-RVR (mm Hg·ml⁻¹·sec⁻¹)</th>
<th>RBF (ml·min⁻¹·100 g⁻¹)</th>
<th>RVR (mm Hg·ml⁻¹·sec⁻¹·100 g⁻¹)</th>
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<td>DR control</td>
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<tr>
<td>Ang II low dose</td>
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<td>DS control</td>
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MABP, mean arterial blood pressure; CO, cardiac output; TPR, total peripheral resistance; Non-RVR, nonrenal vascular resistance; RBF, renal blood flow; RVR, renal vascular resistance; DR, Dahl salt-resistant rats; Ang II, angiotensin II; DS, Dahl salt-sensitive rats. Mean body weight DR rat, 345±21 g; DS rat, 369±9 g. Mean kidney weight DR rat, 3.4±0.3 g; DS rat, 3.2±0.2 g.

*Control DS rat measurements statistically different from control measurements in DR rats (p<0.01).
†Statistically different from control measurements (p<0.01).
in RVR in DR but not in DS rats, and they concluded that DS rats exhibit inappropriately high renal vascular tone during ingestion of excess salt. This inappropriately high vascular tone caused by salt did not result from neurogenic activity because, after section of renal sympathetic nerves or neural stimulation, RVR was similar in DS and DR rats regardless of diet.23 Also, since changes in RVR induced by Ang II were not altered by excess salt intake in either strain and since the renal vascular response to intra-arterial norepinephrine was not altered in DS rats, they further concluded that inappropriately high RVR during excess salt ingestion did not result from increased vascular reactivity to Ang II or norepinephrine. The fact that renal vasodilation resulting from intra-arterial acetylcholine was less in DR rats but unchanged in DS rats given an 8% NaCl diet suggested a failure of DS rats to decrease some functional renal vascular tone caused by excess salt consumption. Fink et al23 concluded that DS rats exert abnormal regulation of renal vascular dilation through local or humoral factors in response to excess salt ingestion.

Grossman et al24 reported that bolus Ang II injections induced a dose-dependent increase in mean blood pressure and RVR and a fall in RBF that were similar in DS and DR rats fed the 0.1% NaCl diet. Mean arterial pressure responses to bolus injections of Ang II were significantly increased only in DS rats given a high salt (8% NaCl) diet; although increases in RVR in response to Ang II injections were greater in both DS and DR rats given a high rather than a low salt diet, there was no difference between the RVR of DS and DR rats. Bolus injections of ET-1 induced dose-dependent increases in mean arterial

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**TABLE 6.** Systemic and Renal Hemodynamic Data After Infusion With Endothelin-1

<table>
<thead>
<tr>
<th>Rat group</th>
<th>MABP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>TPR (mm Hg • ml⁻¹ • sec⁻¹)</th>
<th>Non-RVR (mm Hg • ml⁻¹ • sec⁻¹)</th>
<th>RBF (ml • min⁻¹ • 100 g⁻¹)</th>
<th>RVR (mm Hg • ml⁻¹ • sec⁻¹ • 100 g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR Control</td>
<td>100±3</td>
<td>101±9</td>
<td>59.4±7</td>
<td>73.0±5</td>
<td>608±30</td>
<td>9.9±1.1</td>
</tr>
<tr>
<td>ET-1 low dose</td>
<td>101±8</td>
<td>137±11*</td>
<td>44.2±2*</td>
<td>53.9±2*</td>
<td>796±32*</td>
<td>7.6±0.5*</td>
</tr>
<tr>
<td>ET-1 high dose</td>
<td>100±8</td>
<td>152±10*</td>
<td>39.5±1*</td>
<td>48.4±2*</td>
<td>904±52*</td>
<td>6.6±0.7*</td>
</tr>
<tr>
<td>DS Control</td>
<td>101±2</td>
<td>108±10</td>
<td>56.1±5</td>
<td>77.0±5</td>
<td>897±57†</td>
<td>6.7±2.1†</td>
</tr>
<tr>
<td>ET-1 low dose</td>
<td>101±7</td>
<td>132±10*</td>
<td>45.9±2*</td>
<td>55.0±3*</td>
<td>666±38*</td>
<td>91.±0.4</td>
</tr>
<tr>
<td>ET-1 high dose</td>
<td>101±7</td>
<td>151±13*</td>
<td>40.1±3*</td>
<td>43.8±4*</td>
<td>386±21*</td>
<td>15.7±0.9*</td>
</tr>
</tbody>
</table>

MABP, mean arterial blood pressure; CO, cardiac output; TPR, total peripheral resistance; Non-RVR, nonrenal vascular resistance; RBF, renal blood flow; RVR, renal vascular resistance; DR, Dahl salt-resistant rats; ET-1, endothelin-1; DS, Dahl salt-sensitive rats. Mean body weight DR rat, 281±7 g; DS rat, 305±15 g. Mean kidney weight DR rat, 3.09±0.1 g; DS rat, 3.27±0.2 g.

*Statistically different from control measurements (p<0.01).

†Control DS rat measurements statistically different from control measurements in DR rats (p<0.01).
pressure that were similar in DS and DR rats given low or high salt diets; however, RVR was markedly increased in both DS and DR fed an 8% NaCl diet. Grossman et al.24 concluded that DS rats are not hypersensitive to ET-1 but that salt intake substantially modulates renal vascular reactivity to ET-1. A strict comparison of our studies on Ang II and ET-1 with those of Grossman et al.24 is not warranted since they injected these agents in a bolus that caused elevations in systemic pressure, whereas we infused subpressor doses. It is intriguing to speculate that the ratio of endothelium receptors causing EDRF release to those causing vasoconstriction might be substantially less in renal vasculature of DS than DR rats; such a change in receptor density could possibly explain the differences we observed between RVR in DS and DR rats during infusion of low doses of ET-1 that did not alter blood pressure.

Our findings that nonrenal vasculature of DS and DR rats fed 1% NaCl diets behave similarly in response to vasoactive agents is consistent with previous in vitro studies on rings of thoracic aorta (i.e., nonrenal smooth muscle) from DS and DR rats given a low salt diet that responded similarly to a variety of agonists (acetylcholine, adenosine 5′-diphosphate, thrombin, and nitroprusside).33 Therefore, it seems unlikely that some genetically determined intrinsic abnormality of smooth muscle exists in the aorta and perhaps other nonrenal vessels of prehypertensive DS rats. The fact that no remarkable difference in responses to serotonin or norepinephrine was observed between aortic rings from DS and DR rats given low salt diets34 further supports our findings that in prehypertensive DS rats, nonrenal vessels respond normally to vasoconstrictors.

The findings of others support the concept that a dysfunction of DS kidneys is responsible for inadequate natriuresis that leads to hypertension. It is conceivable that the inability of renal vasodilation that we demonstrated in DS rats might contribute to impaired natriuresis. Renal vascular responses to any of the vasoactive substances we studied could oppose natriuresis in DS rats but would favor natriuresis in DR rats consuming high salt diets. Roman and Kaldunski35 suggested that a reduced glomerular filtration rate in DS rats impairs their ability to excrete sodium at normal levels of renal perfusion pressure. Furthermore, they reported enhanced reabsorption of water and chloride in the loop of Henle of DS rats that contributes to "the resetting of pressure–natriuretic relations." However, additional studies are needed to determine whether other tubular defects exist that might contribute to deficient natriuresis by DS kidneys at normal perfusion pressure.

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