Impaired Renal Vascular Reactivity in Prehypertensive Dahl Salt-Sensitive Rats

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

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 hypertension; 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 coworkers has been especially useful as an animal model for studying experimental hypertension. Some evidence implicates humoral factors, neurogenic mechanisms, and a deficient natriuretic capacity of the kidney as possible causes of salt-induced hypertension. Studies by Dahl et al 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 al 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 al 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 cells play a role in the development of salt-induced hypertension is unclear. Tobian et al, Roman, and Roman and Osborn 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 al 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. Hirata et al 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.

We previously suggested that hypertension that developed in DS rats in response to a high salt diet (8%
A recovery period of 10 minutes was allowed between the two infusion doses.

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 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.

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 technique16-22 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 [RBF] [625 ± 16.8, 619 ± 23.6, and 621 ± 17.7 ml/min] [100 g 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 satu rated KCl solution into the left ventricle, and various organs (kidneys, heart, spleen, and samples of skin and skeletal muscle) were immediately removed. Activities of 57Co, 113Sn, and 46Sc in various tissues were determined with a gamma counter (Packard 5130, Auto-Gamma System, Packard Instrument Co., Downers Grove, Ill.) connected to a multi-channel analyzer (Tracer Northern Co., Middletown, Wis.). Resistance to flow was calculated as the ratio of mean arterial pressure (mm Hg) to RBF, in milliliters per second per 100 grams kidney weight, whereas non-RVR was calculated as the ratio of mean arterial pressure (mm Hg) to [CO–total RBF] (ml/sec). TPR was calculated as the ratio of mean arterial pressure (mm Hg) to CO (ml/sec).

Experimental results are presented as absolute values and also expressed as percentage of change from control values before the first infusions (no measurements were performed during recovery periods):

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

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).

**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. 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. Non-RVR decreased 30% in DS and DR rats (p<0.01), whereas RVR decreased 65% in DR rats (p<0.01) but remained relatively unchanged in DS rats (Figure 3).

Nitroprusside infusion at a subpressor 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 DR and DS 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).

**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·ml⁻¹·sec⁻¹)</th>
<th>Non-RVR (mm Hg·min⁻¹·100 g⁻¹)</th>
<th>RBF (ml·min⁻¹·100 g⁻¹)</th>
<th>RVR (mm Hg·min⁻¹·100 g⁻¹)</th>
<th>Kidney wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR 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>
<td></td>
</tr>
<tr>
<td>DS 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>
<td></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)</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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</thead>
<tbody>
<tr>
<td>DR Control</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>ANP</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>DS Control</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>ANP</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.

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

Ang II infusions at two subpressor doses caused no significant changes in CO, TPR, blood pressure, and non-RVR in DR and DS rats (Table 5 and Figure 4). 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...
We have previously noted that conscious prehypertensive DS rats tended to have a lower baseline RVR than DR rats given a 1% NaCl diet.\textsuperscript{13,17} It is unclear why the RVR was significantly less in DS than DR rats before infusion with vasoactive substances (Table 1). Fink and coworkers\textsuperscript{23} studied RVR and reactivity in autoperfused kidneys of anesthetized female DS and DR rats. Particularly noteworthy was their observation that RVR was also increased 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.\textsuperscript{13,17} It is unclear why the RVR was significantly less in DS than DR rats before infusion with vasoactive substances (Table 1). Fink and coworkers\textsuperscript{23} studied RVR and reactivity in autoperfused kidneys of anesthetized female DS and DR rats. Particularly noteworthy was their observation that RVR was also increased 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.

Table 3 Systemic and Renal Hemodynamic Data After Infusion With Nitroprusside

<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>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 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>

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; NP, nitroprusside; DS, Dahl salt-sensitive rats. Mean body weight DR rat, 367±26 g; DS rat, 361±14 g. Mean kidney weight DR rat, 3.26±0.2 g; DS rat, 3.38±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).

The RS, 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>
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<tr>
<td>DR 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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>DS 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>
</tr>
<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>
</tr>
<tr>
<td>NE high dose</td>
<td>105±7</td>
<td>128±9</td>
<td>49.2±1</td>
<td>53.4±4</td>
<td>330±26†</td>
<td>19.1±1.4†</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; 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.

*Control DS rat measurements statistically different from control measurements in DR rats (p<0.01).
†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 can play a significant role in the regulatory mechanism of blood pressure and vascular output. Guanylate cyclase, resulting from 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 non-heme-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. Activation of either soluble or particulate guanylate cyclase will increase intracellular cGMP, which activates protein kinase and causes a vasodilatory response. ANP and nitroprusside are therefore dilators. Norepinephrine and Ang II bind to specific receptors that cause influx of calcium and vasoconstriction. Although ET-1 is considered an endothelium-derived vasoconstrictor polypeptide, it can, in low concentration, cause vasodilation in the perfused mesenteric artery of the rat. In low dosage, intravenous bolus injections of endothelin can also decrease systemic and RVR in anesthetized cats. Vasodilation results mainly from release of EDRF that we observed in both DS and DR rats. Intra-arterial acetylcholine infusion caused a greater increase in RVR in DS than DR rats; however, the response to intra-arterial norepinephrine infusion was similar in DS and DR rats. Intra-arterial acetylcholine infusion caused a greater decrease in RVR in DR than DS rats. Our results with intravenous infusions of Ang II and vasodilators (ANP or nitroprusside) were similar to those of Fink et al; why renal vasculature of DS rats was hyperresponsive to norepinephrine in our current study but not in that of Fink et al, is unclear. The use of intrarenal pressor doses by Fink et al rather than intravenous subpressor doses may have masked a hypersensitivity of the renal vasculature in DS rats. They also reported that eating an 8% NaCl diet for 4 weeks caused a significant decrease

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

<table>
<thead>
<tr>
<th>Rat group</th>
<th>MABP (mm Hg)</th>
<th>CO (ml/min)</th>
<th>TPR (mm Hg·min⁻¹·100 g⁻¹)</th>
<th>Non-RVR (mm Hg·min⁻¹·100 g⁻¹)</th>
<th>RBF (ml·min⁻¹·100 g⁻¹)</th>
<th>RVR (mm Hg·min⁻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±1</td>
<td>127±4</td>
<td>48.7±2</td>
<td>56.1±3</td>
<td>490±26</td>
<td>12.6±0.6</td>
</tr>
<tr>
<td>Ang II low dose</td>
<td>100±4</td>
<td>133±12</td>
<td>45.1±3</td>
<td>52.1±2</td>
<td>520±46</td>
<td>11.5±0.9</td>
</tr>
<tr>
<td>Ang II high dose</td>
<td>100±6</td>
<td>138±12</td>
<td>43.5±1</td>
<td>49.5±3</td>
<td>489±28</td>
<td>12.3±0.5</td>
</tr>
<tr>
<td>DS</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>105±4</td>
<td>136±10.8</td>
<td>46.3±6</td>
<td>55.1±5</td>
<td>678±59</td>
<td>9.3±1.3*</td>
</tr>
<tr>
<td>Ang II low dose</td>
<td>100±7</td>
<td>131±11</td>
<td>45.8±4</td>
<td>52.3±5</td>
<td>512±36†</td>
<td>11.7±0.8†</td>
</tr>
<tr>
<td>Ang II high dose</td>
<td>101±6</td>
<td>132±10</td>
<td>45.9±2</td>
<td>49.2±4</td>
<td>275±18†</td>
<td>22.1±1.0†</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; 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).
Table 6. Systemic and Renal Hemodynamic Data After Infusion With Endothelin-1

<table>
<thead>
<tr>
<th>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>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>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>
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<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>
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<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</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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).

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. 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

Figure 5. Bar graphs show effect of endothelin-1 (ET-1) on cardiac output, total peripheral resistance (TPR), and nonrenal and renal vascular resistance of Dahl salt-resistant (DR) and salt-sensitive (DS) rats. Upper graph is the lower infusion rate and the bottom graph is the higher infusion rate. Results are expressed as percentage of change from control. Vertical lines indicate standard deviation.
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 EDHF 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 (acyetylcholine, 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 diets\(^34\) 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 Kaldunski\(^35\) 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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Impaired renal vascular reactivity in prehypertensive Dahl salt-sensitive rats.
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