Effects of Interstrain Renal Transplantation on NaCl-Induced Hypertension in Dahl Rats

Donald A. Morgan, Gerald F. DiBona, and Allyn L. Mark

Previous studies using renal transplantation suggested that the genotype of a homograft kidney plays the primary role in determining chronic arterial pressure levels in Dahl salt-sensitive (DS) and salt-resistant (DR) rats, but this conclusion derived largely from observations during low NaCl diet. Recent studies indicate that extrarenal factors, including the sympathetic nervous system, play a critical role in the development of NaCl-induced hypertension in DS rats. To assess the contribution of extrarenal and renal factors in the development of NaCl-induced hypertension in Dahl rats, we performed renal transplantation in DS and DR rats. Both kidneys of the recipient were removed at the time of transplantation. Four groups of rats (n=18-23 in each group) were fed a high NaCl (8.0%) diet for 2 weeks after renal transplantation. These included DR_R, DR_S, DS_R, and DS_S, where DR or DS indicates the recipient strain and the subscript indicates the homograft strain. Mean arterial pressure was measured from the femoral artery in conscious rats. On a high NaCl diet, mean arterial pressure was significantly lower (p<0.05) in DR_R (103±2 mmHg; mean±SEM) compared with DR_S (145±5 mmHg), DS_R (151±7 mmHg), and DS_S (160±5 mmHg). The finding that DR rats with a DS kidney (DR_S) developed hypertension during high NaCl diet confirms the concept that the kidney plays an important hypertensinogenic role in the Dahl strain. The fact that DS rats with a DR kidney (DS_R) also developed hypertension indicates that extrarenal factors also contribute significantly to NaCl-induced hypertension in DS rats. (Hypertension 1990;15:436-442)

Dahl et al 1-4 developed two inbred strains of rats with a contrasting blood pressure response to high NaCl diet: a salt-sensitive (DS) strain and a salt-resistant (DR) strain. Based on studies using interstrain renal transplantation, Dahl and colleagues5-7 proposed that the kidneys have a "decisive, genetically determined influence on the development of both NaCl and renal hypertension." In support of this concept, other studies have shown that the kidneys from DS rats exhibit impaired intrinsic natriuretic capacity,8 lower renal papillary blood flow,9 and lower antihypertensive influence10 than do kidneys from DR rats. From studies involving parabiosis,11-13 Dahl and associates reported that humoral substances also played a critical role in NaCl-induced hypertension in the DS strain. These investigators proposed that these substances were linked to the kidney. Thus, despite evidence that DS and DR rats have genetic differences in adrenal steroidogenesis (i.e., extrarenal factors) that contribute to abnormal control of blood pressure in DS rats,14-16 Dahl and Heine7 in 1975 advanced the concept that the "genotype of the homograft kidneys plays the primary role in determining chronic blood pressure levels in two strains of rats with opposite genetically controlled propensities for hypertension." However, subsequent studies provided evidence that abnormalities in the sympathetic nervous system may contribute importantly to NaCl-induced hypertension in DS rats.17-24 Thus, there is now additional evidence for a critical role of extrarenal as well as renal mechanisms in the DS rats.

In reviewing the previous studies on blood pressure effects of renal transplantation in Dahl rats,5-7 we found that most of the conclusions had derived from experiments in rats fed a low NaCl diet. Accordingly, we reexamined the contribution and interrelation of renal and extrarenal factors in the development of NaCl-induced hypertension in DS and DR rats. We reevaluated effects of interstrain renal transplantation in DS and DR rats fed low (0.4%) and high (8.0%) NaCl diet.

Methods

Animals

The animals used in the study were female DS (n=244) and DR (n=205) rats obtained from the
Brookhaven National Laboratories, Upton, New York. Rats were fed tap water and a low NaCl diet (0.4% NaCl and 1.3% KCl per unit of dry weight) ad libitum from a few days after weaning until 7–8 weeks of age. The care and study of the rats complied with the guiding principles for animal experimentation of the American Physiology Society and were approved by the institutional committee on animal experimentation.

Renal Transplantation

The technique used to perform renal transplantation was similar to the methods used by Dahl et al.,1-7 which was a modification of the technique described by Lee and colleagues.25,26 The renal transplantation was performed on a temperature-controlled surgical table that was positioned beneath a stereoscopic microscope (Olympus UMZ, Lake Success, New York). The microscope was attached to a boom that enabled the magnified field (×5–20) to be shifted between the donor and recipient rats as needed. Clean dissecting instruments were used.

When the Dahl rats had reached 7–8 weeks of age, a pair of rats was brought to the surgical laboratory. One of the rats was selected to be the donor. The donor rat was anesthetized with methohexital sodium (Brevital, Eli Lilly and Co., Indianapolis, Indiana) at a dose of 40 mg/kg i.p. When the rat was anesthetized, the femoral vein was cannulated (PE-50). Anesthesia was maintained throughout the surgery by repeated intravenous administration of methohexital sodium (total maintenance dose less than 30 mg/kg). A midline abdominal incision was made and the left renal area (kidney, renal artery and vein, ureter) and adjacent segments (approximately 4–5 mm in length) of abdominal aorta and inferior vena cava were exposed. The left ureter was isolated and then cannulated (PE-10). Next, the distal end of the abdominal aorta was ligated with 4.0 silk suture. To protect the donor kidney from any damage, the left renal area was covered with a warm, moist gauze.

The recipient rat was then anesthetized with methohexital sodium. Again, the left renal area was exposed with a midline abdominal incision. Next, the left ureter was sectioned 1–1.5 mm below the left kidney. The left renal artery and vein were ligated (4.0 silk), and the left kidney was carefully removed. The abdominal aorta and inferior vena cava just caudal to the left renal artery and vein were separated and freed from connective tissue for a length of 15–20 mm. As before, the left renal area of the recipient rat was covered with a warm, moist gauze.

The abdominal aorta of the donor was then clamped above the right renal artery, and the segment of aorta perfusing the left kidney was slowly flushed with 2–3 cc cold Ringer's lactate solution (2°–4°C). Segments of the aorta and inferior vena cava with the attached left renal artery and vein, respectively, were then removed and the left kidney immersed in cold (2°–4°C) oxygenated Ringer's lactate solution. Finally, the donor rat was killed.

With the left kidney of the recipient rat already removed, blood flow through segments of the abdominal aorta and inferior vena cava was interrupted by using a vascular clamp. The donor kidney was removed from the cold oxygenated Ringer's lactate and placed in the recipient's abdomen. A small incision (2–3 mm) was made in the recipient's aorta. Using a monofilament nylon 8.0 suture with a ¾-circle taper needle (Ethicon, Somerville, New Jersey), the two aortic segments (donor and recipient) were anastomosed end to side. An oval section of the donor's inferior vena cava, and the donor and recipient vena cava were anastomosed end to side. The vascular clamps were slowly removed, and blood flow was restored to the transplanted kidney. Total time of renal ischemia was between 40 and 60 minutes. When the kidney regained and maintained its normal color, urine began to flow starting several minutes after restoration of perfusion. As soon as urine flow resumed, the donor and recipient ureters were anastomosed over an indwelling PE-10 tubing. The transplanted kidney was sutured to the underlying abdominal muscles to secure it in place. The recipient's right kidney was removed when the transplanted kidney began to function, and the abdominal incision was closed. Each rat was given an antibiotic (oxytetracycline, 100 mg/kg i.m.) and allowed to recover in an individual cage with periodic observation. Immunosuppressive drugs were not administered. If the rat showed any signs of postoperative stress or illness, it was immediately killed with an overdose of methohexital sodium.

Experimental Protocol

Four groups of Dahl rats underwent renal transplantation: group 1, recipient DR rat with a transplanted resistant (R) kidney (DRR); group 2, recipient DR rat with a transplanted sensitive (S) kidney (DRS); group 3, recipient DS rat with a transplanted R kidney (DSR); group 4, recipient DS rat with a transplanted S kidney (DSS).

For 2 weeks after transplantation, rats were fed either a low NaCl diet (0.4% NaCl: DRR, n=10; DRS, n=10; DSR, n=11; and DSS, n=11) or a high NaCl diet (8.0% NaCl: DRR, n=20; DRS, n=23; DSR, n=18; DSS, n=20). After 2 weeks of these diets, rats were anesthetized with methohexital sodium (40 mg/kg i.p.). A femoral arterial and two femoral venous cannulae were inserted, tunneled subcutaneously, externalized at the dorsum of the neck, filled with heparinized saline, and plugged with stainless steel pins. Each rat was allowed to recover for 24–36 hours in an individual cage.

On the day of experimentation, the rat's arterial catheter was connected to a low-volume pressure transducer (CP-01, Century Technology Co., Inglewood, California) that was placed at the same level as the rat's heart. The systemic arterial pressure signal was directed to two couplers (Beckman 9853A, Beckman Co., Schiller Park, Illinois) for measurements of phasic and mean arterial pressure and to a cardiotra-
Data Analysis

Renal Histology

were continuously recorded throughout the study. At weeks before study.

with methohexital sodium (20–25 mg/kg i.v.). One

x1

considered significant. The Pearson

values less than 0.05 were

p

for multiple comparison;

438

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Hypertension

TABLE 1. Arterial Pressure and Heart Rate in Dahl Renal Transplanted Rats Fed Low and High NaCl Diet

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>SAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low NaCl (0.4%) diet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRr</td>
<td>10</td>
<td>130±6</td>
<td>79±3</td>
<td>96±3</td>
<td>459±13</td>
</tr>
<tr>
<td>DSr</td>
<td>10</td>
<td>144±4</td>
<td>90±4</td>
<td>108±4</td>
<td>451±14</td>
</tr>
<tr>
<td>DSR</td>
<td>11</td>
<td>138±4</td>
<td>80±2</td>
<td>99±2</td>
<td>430±17</td>
</tr>
<tr>
<td>DDS</td>
<td>11</td>
<td>160±5</td>
<td>97±3</td>
<td>119±3</td>
<td>417±10</td>
</tr>
<tr>
<td><strong>High NaCl (8.0%) diet</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDr</td>
<td>20</td>
<td>138±3</td>
<td>86±3</td>
<td>103±2</td>
<td>439±9</td>
</tr>
<tr>
<td>DSR</td>
<td>23</td>
<td>188±7</td>
<td>123±5</td>
<td>145±5</td>
<td>447±11</td>
</tr>
<tr>
<td>DSS</td>
<td>18</td>
<td>202±9</td>
<td>124±7</td>
<td>151±7</td>
<td>465±8</td>
</tr>
<tr>
<td>DDS</td>
<td>20</td>
<td>214±7</td>
<td>133±5</td>
<td>160±5</td>
<td>460±12</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Results of statistical analysis are presented in text and Figures 1 and 2. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate in beats per minute.

Uninephrectomy

In addition to the rats that had undergone renal transplantation, we also studied DR and DS rats that had undergone right nephrectomy and were fed either low NaCl (DRn, n=6 and DSn, n=10) or high NaCl (DRun, n=13 and DSun, n=10) diet for 2 weeks before study.

Renal Histology

After fixation and embedding, 2 μm coronal sections from each kidney were made and stained with hematoxylin-eosin and periodic acid-Schiff techniques. They were coded by one investigator (D.A.M.) and reviewed by a different investigator (G.F.D.) who had no knowledge of the code.

Data Analysis

Statistical analyses were performed using unpaired t test and analysis of variance with Bonferroni method for multiple comparison; p values less than 0.05 were considered significant. The Pearson χ² test was used to compare mortality between groups and also to compare mortality in rats with transplanted S versus R kidneys. Results are expressed as mean±SEM.

Results

Effects of Interstrain Renal Transplantation in Dahl Salt-Resistant and Salt-Sensitive Rats Fed Low (0.4%) NaCl Diet (Tables 1 and 2, Figure 1)

All four groups of rats (DRr, DRs, DSS, and DSR) gained weight during the 2 weeks after transplantation and appeared healthy at the time of study (Table 2). Also, each of the four groups of rats had normal plasma urea nitrogen, creatinine, sodium, and potassium concentrations with no differences between groups in these variables (Table 2). Kidney weights and cardiac ventricular weight did not differ significantly in the four groups (Table 2).

Mean arterial pressure was significantly higher (p<0.05) in DSS (119±3 mm Hg) than in DRr (96±3 mm Hg) and DSR (99±2 mm Hg) (Figure 1 and Table 1). Thus, an R kidney lowered mean arterial pressure in DS rats fed a low NaCl diet. There was no significant correlation between plasma creatinine concentration and mean arterial pressure in these four groups. Heart rate did not differ in the four groups (Table 1).

Effects of Interstrain Renal Transplantation in Dahl Salt-Resistant and Salt-Sensitive Rats Fed a High (8.0%) NaCl Diet

Rats fed a high NaCl diet did not gain significant weight during the 2 weeks after transplantation, but there was no significant difference in body weights in the four groups (Table 2). Moreover, plasma urea nitrogen, creatinine, sodium, and potassium concentrations did not differ significantly between groups (Table 2). Kidney weights did not differ significantly in the four groups (Table 2). Cardiac ventricular weight was lower (p<0.05) in DRr than in the other three groups (Table 2).

During high NaCl diet, mean arterial pressure was lower (p<0.05) in DRr (103±2 mm Hg) than in the other three groups (Figure 2 and Table 1). Two findings are of particular note. First, mean arterial
pressure was higher \((p<0.05)\) in DS \(_R\) (151 ± 7 mm Hg) than in DR \(_R\) (103 ± 1 mm Hg) (Figure 2 and Table 1). Second, mean arterial pressure did not differ significantly in DS \(_R\) (151 ± 7 mm Hg) and DR \(_S\) (145 ± 5 mm Hg). Thus, during high NaCl diet an S kidney promoted significant hypertension in DR rats. However, DS rats with an R kidney also developed significant hypertension during high NaCl diet. During high NaCl diet, there was no significant correlation between plasma creatinine concentration and mean arterial pressure in these four groups. Heart rate did not differ among the four groups (Table 1).

**Effects of Uninephrectomy in Dahl Salt-Resistant and Salt-Sensitive Rats**

In DR rats after uninephrectomy, mean arterial pressure was 104 ± 2 mm Hg during low NaCl diet and 105 ± 2 mm Hg during high NaCl diet (Table 3). These values did not differ significantly from corresponding values in DR \(_R\) rats (Tables 1 and 3). Kidney weights also did not differ significantly in DR rats with uninephrectomy versus DR \(_R\) on either low or high NaCl diets (Tables 2 and 3). In DS rats after uninephrectomy, mean arterial pressure was 114 ± 4 mm Hg during low NaCl diet and 124 ± 5 mm Hg after 2 weeks of high NaCl diet (Table 3). During low NaCl diet, mean arterial pressure in the DS rats with uninephrectomy did not differ from that in DS \(_R\) rats (Tables 1 and 3). However, during high NaCl diet, mean arterial pressure was lower \((p<0.05)\) in DS rats with uninephrectomy than in DS \(_S\) rats (Tables 1 and 3). Kidney weights were lower \((p<0.05)\) in DS rats with uninephrectomy than in DS \(_R\) rats on both low and high NaCl diets (Tables 2 and 3).

**Mortality Data**

In the rats fed a low NaCl diet, the mortality during the 2 weeks after transplantation tended to be lower in DR \(_R\) but did not differ significantly among the groups: DR \(_R\) (2 of 12 or 16.7%), DR \(_S\) (11 of 21 or 52.4%), DS \(_R\) (11 of 22 or 50.0%), and DS \(_S\) (6 of 17 or 35.3%). In the rats fed a high NaCl diet, the mortality also did not differ significantly among the groups: DR \(_R\) (9 of 29 or 31.0%), DR \(_S\) (17 of 40 or 42.5%), DS \(_R\) (18 of 38 or 47.4%), and DS \(_S\) (8 of 26 or 30.8%). There was, however, a difference of borderline statistical significance \((p=0.053)\) in mortality between Dahl rats with a transplanted S kidney (57 of 133 or 42.9%) versus a transplanted R kidney (25 of 84 or 29.8%).

**Results of statistical analysis are presented in text. BUN, blood urea nitrogen concentration; Cr, plasma creatinine concentration; DR\(_R\), Dahl salt-resistant rat with a transplanted resistant kidney; DR\(_S\), Dahl salt-resistant rat with a transplanted sensitive kidney; DS\(_R\), Dahl salt-sensitive rat with a transplanted resistant kidney; DS\(_S\), Dahl salt-sensitive rat with a transplanted sensitive kidney.**

**FIGURE 1.** Mean arterial pressure (MAP) in Dahl salt-resistant (DR) and salt-sensitive (DS) rats with a transplanted resistant (R) or sensitive (S) kidney fed low NaCl diet (0.4% NaCl) for 2 weeks after renal transplantation.
MAP (mmHg)

n = 20
n = 23
n = 20
n = 18

P<0.05
P<0.05
P<0.05

FIGURE 2. Mean arterial pressure (MAP) in Dahl salt-resistant (DR) and salt-sensitive (DS) rats with a transplanted resistant (R) or sensitive (S) kidney fed high NaCl diet (8.0% NaCl) for 2 weeks after renal transplantation.

Renal Histology

The predominant histological features were characteristic of hypertensive renal structural alterations. These changes consisted of medial thickening and intimal fibrous proliferation leading to reduction of the lumen of small arteries and arterioles. In areas where complete occlusion of the lumen was observed, there were surrounding areas of tubular atrophy and interstitial fibrosis with scant mononuclear cell infiltration. Adjacent glomeruli showed wrinkling of the capillary tuft with thickening of the capillary walls progressing to shrinkage of the tuft. These changes were more pronounced in rats fed a high NaCl diet that had elevated mean arterial pressure (DR<sub>S</sub>, DS<sub>R</sub>, and DS<sub>S</sub>). Similar changes of slightly less magnitude were observed in uninephrectomized DS rats on high NaCl diet. There were no vascular or glomerular changes indicative of rejection.

Discussion

The principal finding in this study was that DS<sub>R</sub> rats developed significant NaCl-induced hypertension. This observation indicates that extrarenal factors contribute substantially to NaCl-induced hypertension in DS rats. The study also confirms previous reports that renal mechanisms contribute importantly to control of blood pressure in Dahl rats. During low NaCl diet, an R kidney lowered blood pressure in DS rats. In addition, during high NaCl diet, DR<sub>R</sub> rats developed hypertension.

Renal Versus Extrarenal Mechanisms

Our study confirms previous reports that the genotype of the kidney plays an important role in determining blood pressure in Dahl rats.<sup>5-7</sup> Indeed, our data support Dahl's observations that "hypertension" during low NaCl diet in Dahl rats is mainly of renal origin. An S kidney raised blood pressure in DR rats during low and high NaCl diet. This prohypertensive influence of an S kidney has been attributed to several mechanisms including impaired natriuresis,<sup>8</sup> release or activation of a prohypertensive humoral substance,<sup>11-13</sup> and deficiency of an antihypertensive factor possibly emanating from the renal medullary interstitial cells.<sup>10</sup>

The main thrust of our study compared with previous studies of interstrain renal transplantation in Dahl rats is that extrarenal factors contribute significantly to NaCl-induced hypertension in DS rats. This conclusion was prompted by the finding that DS<sub>R</sub> developed

### Table 3. Body Weights, Arterial Pressure, and Renal Function in Uninephrectomized Dahl Rats Fed Low and High NaCl Diet

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Body weight (g)</th>
<th>Preop weight</th>
<th>Study weight</th>
<th>SAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>BUN (mg/dl)</th>
<th>Cr (mg/dl)</th>
<th>Plasma Na&lt;sup&gt;+&lt;/sup&gt; (meq/l)</th>
<th>Plasma K&lt;sup&gt;+&lt;/sup&gt; (meq/l)</th>
<th>Kidney weight (g/100 g body wt)</th>
<th>Ventricular weight (g/kg body wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low NaCl (0.4%) diet</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DR&lt;sub&gt;un&lt;/sub&gt;</td>
<td>6</td>
<td>152±3</td>
<td>170±3</td>
<td>134±7</td>
<td>89±9</td>
<td>104±2</td>
<td>427±11</td>
<td>21±0.8</td>
<td>0.5±0.04</td>
<td>152±1.9</td>
<td>4.1±0.2</td>
<td>0.68±0.03</td>
<td>0.76±0.01</td>
<td></td>
</tr>
<tr>
<td>DS&lt;sub&gt;um&lt;/sub&gt;</td>
<td>10</td>
<td>184±3</td>
<td>208±4</td>
<td>158±6</td>
<td>94±3</td>
<td>114±4</td>
<td>430±7</td>
<td>20±2.0</td>
<td>0.6±0.1</td>
<td>149±0.9</td>
<td>3.9±0.7</td>
<td>0.53±0.02</td>
<td>0.80±0.01</td>
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</tr>
<tr>
<td><strong>High NaCl (8.0%) diet</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DR&lt;sub&gt;un&lt;/sub&gt;</td>
<td>13</td>
<td>190±4</td>
<td>210±4</td>
<td>140±4</td>
<td>88±5</td>
<td>105±2</td>
<td>441±11</td>
<td>28±2.0</td>
<td>0.6±0.1</td>
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<td>124±6</td>
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<td>3.9±0.7</td>
<td>0.67±0.03</td>
<td>0.88±0.04</td>
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</tr>
</tbody>
</table>

Values are mean±SEM. Results of statistical analysis are presented in text. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial blood pressure; HR, heart rate in beats per minute; BUN, blood urea nitrogen concentration; Cr, plasma creatinine concentration; DR<sub>un</sub>, Dahl salt-resistant rat that had undergone right nephrectomy; DS<sub>um</sub>, Dahl salt-sensitive rat that had undergone right nephrectomy.
significant NaCl-induced hypertension. Before con-
cluding that this finding indicated an important role for
extranuclear mechanisms in the DS rats, we considered
alternative explanations for this observation.

One mechanism for the NaCl-induced hyperten-
sion in DS_R might be renal damage from the trans-
plantation or rejection. This seems improbable for
several reasons. Values for BUN and plasma crea-
tinine concentration in DS_R were not elevated and did
not differ significantly from the other groups. There
was no significant correlation between mean arterial
pressure and plasma creatinine concentration in the
DS_R rats. Moreover, DR_R rats that underwent the
same transplantation procedure as DS_R did not
develop NaCl-induced hypertension. Therefore,
NaCl-induced hypertension in DS_R cannot be
explained solely by renal damage secondary to the
transplantation. In addition, there was no histological
or functional evidence of significant rejection.

An alternative mechanism in interpreting our data
is the question of selective mortality. In animals
studied at the end of the high NaCl diets, we found
no significant differences in arterial pressure in DS_R,
DS_S, and DS_S rats (Figure 2). It might be argued that
this finding was biased by the possibility that rats with
more severe hypertension died before study and that
these premature deaths were more frequent in some
groups (e.g., DS_S) than in others. If true, then the
surviving rats studied at the end of the high NaCl
diets might not be representative of the groups.
There was no significant difference in mortality
among the groups fed the high NaCl diet. This would
speak against an influence of selective mortality on
our data. However, we should indicate that our data
do not permit a precise quantitative comparison of the
rapidity and magnitude of NaCl-induced hyper-
tension in the three groups. This comparison would
require serial measurements of arterial pressure in the
conscious state over several weeks beginning at the
time of transplantation. Thus, our data do not
necessarily indicate that NaCl-induced hypertension
in DS_R is as rapid or severe as in DS_S or DR_R rats.
The point we wish to emphasize is not a quantitative
comparison of the hypertension in DS_R, DS_S, and
DR_R rats, but rather the fact that DS_S rats developed
significant NaCl-induced hypertension (when com-
pared with DR_R rats). It seems highly improbable
that this important finding can be explained by
selective mortality as the mortality rate in DS_S and
DR_R rats was similar (31% in each group).

Dahl concluded from his observations that the
kidney was the decisive influence in NaCl-induced hy-
pertension.5-7 Our data indicate that extranuclear
factors can also exert a decisive influence. At first
stance, our findings would seem inconsistent with
Dahl's work, but a careful review of his studies
indicates that his observations are not inconsistent
with our data. First, most of Dahl's observations
during renal transplantation were performed during
low NaCl diet.5-7 Our findings during low NaCl diet
are generally similar to Dahl's results and his conclu-
sion that the kidney plays the primary role in deter-
miming chronic blood pressure level. Second, Dahl's
limited observations in rats with renal transplanta-
tion fed high NaCl diet are not inconsistent with our
conclusion. Dahl found that all four groups of rats
with renal transplant (DR_R, DS_R, DS_S, and DS_S)
developed hypertension during high NaCl diet.6 He
concluded that this was caused by the combination of
high NaCl diet and renal injury from the transplanta-
tion. Because all four groups developed NaCl-induced
hypertension, it is difficult to interpret these studies in
terms of the role of renal and extrarenal factors. In our
experiments, DR_R rats fed the high NaCl diet remained
normotensive. The fact that the DR_R rats remained
normotensive whereas DS_S rats developed hyperten-
sion permits the conclusion that extrarenal factors
contribute importantly to NaCl-induced hypertension
in DS rats. From these experiments, we cannot identify
the precise extrarenal mechanisms that might be impli-
cated, but previous experiments suggest a possible role
for adrenal steroidogenesis, humoral factors, and the
sympathetic nervous system.

Uninephrectomy Versus Transplantation

During low NaCl diet, blood pressure did not differ
between DS rats with uninephrectomy and DS_R rats
(Table 1 and 3). However, during high NaCl, the
DS_S rats developed more hypertension than the DS
rats with uninephrectomy (Tables 1 and 3). The
kidneys from DS_S rats were heavier (p<0.05) than
the kidneys from DS rats with uninephrectomy on
both low and high NaCl diets. In contrast, blood
pressure did not differ in DR rats with uninep-
rectomy and DR_R rats even during high NaCl diet
(Table 1 and 3). These data indicate that the
transplantation procedure per se has some prohy-
tensive effect. We presume that this influence was
due to renal structural or functional changes related
to the transplantation procedure. It is important to
note that this prohypertensive influence of transplanta-
tion was manifest only in DS rats fed a high NaCl
diet. In other words, the prohypertensive influence
of transplantation depended on an interaction with
dietary and genetic factors. Can this prohypertensive
influence of transplantation explain the principal
finding of our study, which is that DS_S rats develop
NaCl-induced hypertension? In other words, does
damage to the R kidney during transplantation pro-
mote hypertension or eliminate the normal antihy-
pertensive influence of the R kidney? DR_R rats
remained normotensive during low and high NaCl
diet (Table 1). This suggests that the transplantation
procedure does not eliminate the antihypertensive
influence of the R kidney. Thus, the development
of NaCl-induced hypertension in DS_S cannot be
explained by the transplantation procedure. It must
reflect, instead, a role for extrarenal mechanisms.
However, the precise contribution of extrarenal ver-
sus renal mechanisms to the NaCl-induced hyperten-
sion, independent of the effects of the transplanta-
Mortality Data

There was substantial mortality during the 2 weeks after transplantation. This mortality did not differ significantly among the four groups during high NaCl diet. Thus, as discussed previously, it seems unlikely that the mortality among groups biased our conclusions regarding the role of renal and extrarenal factors in the NaCl-induced hypertension. It should be noted, however, that across groups rats with a transplanted S kidney had a higher mortality than rats with a transplanted R kidney (42.9% vs. 29.8%, respectively; p=0.053). We cannot determine from the present study if the adverse effect of an S kidney on mortality was related to its effect on blood pressure or to an effect that is independent of blood pressure.

In summary, the present study indicates that DRs and DSr rats both develop hypertension during high NaCl diet. The former observation confirms the concept that the kidney plays an important prohypertensive role in the Dahl strain. The latter observation indicates that extrarenal factors also contribute importantly to NaCl-induced hypertension in DS rats.

Acknowledgments

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References


KEY WORDS • sodium-dependent hypertension • transplantation, homologous • salt • Dahl rats
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Does not reduce cardiac output² and is not commonly associated with orthostasis, constipation and impotence.† Efficacy and tolerability similar in younger and older patients.

### EFFECTS OF VARIOUS CALCIUM ANTAGONISTS³

<table>
<thead>
<tr>
<th>RELAXES THE VESSELS</th>
<th>CARDENE</th>
<th>Nifedipine</th>
<th>Diltiazem</th>
<th>Verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASOSELECTIVITY</td>
<td>++++</td>
<td>+++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Systemic</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vasodilatory Side Effects</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Myocardial Depression</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Blocks AV Conduction</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Nonvascular Smooth Muscle Side Effects</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+++*</td>
</tr>
<tr>
<td>Safe for Concomitant Use w/β-blockers</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are based on a scale from 0 to ++++, where 0 = least and ++++ = most. Adapted from Pepine³

†Due to peak/trough variability with CARDENE, it is consistent with good medical practice to measure blood pressure at trough (8 hours after dosing) and at peak (1-2 hours after dosing). During clinical trials, peak effects of CARDENE were not associated with increased side effects. With CARDENE treatment, blood pressures were significantly reduced throughout the dosing interval compared to placebo.

‡Most common side effects include flushing, headache, dizziness and pedal edema.

*Particularly constipation in the elderly.

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**CONTRAINDICATIONS:** Patients with hypersensitivity to the drug. Because part of the effect of CARDENE is secondary to reduced afterload, the drug is also contraindicated in patients with aortic stenosis.

**WARNINGS:** Increased Angina: About 7% of patients in short-term placebo-controlled angina trials have developed increased frequency, duration or severity of angina on starting CARDENE, or at the time of dosage increases, compared with 4% of patients on placebo. Comparisons with beta-blockers also show a greater frequency of increased angina, 4% vs 1%. The mechanism of this effect has not been established. (See ADVERSE REACTIONS.)

**Use in Patients with Congestive Heart Failure:** Although preliminary hemodynamic studies in patients with congestive heart failure have shown that CARDENE reduced afterload without impairing myocardial contractility, it has a negative inotropic effect in vitro and in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker.

**Beta-Blocker Withdrawal:** CARDENE is not a beta-blocker and gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8-10 days.

**PRECAUTIONS:** General: Blood Pressure: Careful monitoring of blood pressure during the initial administration and titration of CARDENE is suggested. Patients with CHF may occasionally produce symptomatic hypotension. Caution is advised to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage. Because of prominent effects at the time of peak blood levels, initial titration should be performed with measurements of blood pressure at trough (just before the next dose) and at peak effect (1-2 hours after dosing).

**Drug Interactions:** Cimetidine: Cimetidine increases CARDENE plasma levels. Patients receiving the two drugs concomitantly should be carefully monitored.

**Dosage and Administration:** CARDENE is not a beta-blocker and gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8-10 days.
Effects of interstrain renal transplantation on NaCl-induced hypertension in Dahl rats.
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