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

DRg, DS

and DSs, 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 DRg (103±2 mmHg; mean±SEM) compared with DRs (145±5 mm Hg), DSg (151±7 mm Hg), and DSs (160±5 mm Hg). The finding that DR rats with a DS kidney (DRs) 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 (DSg) also developed hypertension indicates that extrarenal factors also contribute significantly to NaCl-induced hypertension in DS rats. (Hypertension 1990;15:436-442)

Dahl et al1-4 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
Renal Transplantation

The technique used to perform renal transplantation was similar to the methods used by Dahl et al.,5-7 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 were exposed. The left renal artery and vein were ligated 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 3/8-circle taper needle (Ethicon, Somerville, New Jersey), the two aortic segments (donor and recipient) were anastomosed end to side. An oval section was then removed from the recipient'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 (oxtetracycline, 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 cardiota-
were continuously recorded throughout the study. At 2 weeks before study.

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 (DR, DR, DS, and DS) 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 DS (119±3 mm Hg) than in DRR (96±3 mm Hg) and DS (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 DR than in the other three groups (Table 2).

During high NaCl diet, mean arterial pressure was lower (p<0.05) in DR (103±2 mm Hg) than in the other three groups (Figure 2 and Table 1). Two findings are of particular note. First, mean arterial
Effects of Renal Transplantation on Blood Pressure

Morgan et al

Table 2. Body Weight and Renal Function in Dahl Renal Transplanted Rats Fed Low and High NaCl Diet

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Kidney weight (g/kg body wt)</th>
<th>Ventricular weight (g/kg body wt)</th>
<th>BUN (mg/dl)</th>
<th>Cr (mg/dl)</th>
<th>Plasma Na+ (meq/l)</th>
<th>Plasma K+ (meq/l)</th>
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<tr>
<td><strong>Low NaCl (0.4%) diet</strong></td>
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<tr>
<td>DRₐ</td>
<td>10</td>
<td>187±6</td>
<td>205±4</td>
<td>0.67±0.03</td>
<td>0.74±0.02</td>
<td>24±1.0</td>
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<td>DRₕ</td>
<td>10</td>
<td>181±6</td>
<td>203±5</td>
<td>0.84±0.05</td>
<td>0.79±0.02</td>
<td>25±2.0</td>
<td>1.1±0.2</td>
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<td>DSₐ</td>
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<td>183±4</td>
<td>202±5</td>
<td>0.80±0.02</td>
<td>0.83±0.04</td>
<td>20±1.2</td>
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<td>DSₕ</td>
<td>11</td>
<td>187±5</td>
<td>201±3</td>
<td>0.92±0.09</td>
<td>0.84±0.03</td>
<td>27±4.0</td>
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<td><strong>High NaCl (8.0%) diet</strong></td>
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<tr>
<td>DRₐ</td>
<td>20</td>
<td>187±5</td>
<td>197±6</td>
<td>0.78±0.04</td>
<td>0.79±0.03</td>
<td>28±3.0</td>
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<tr>
<td>DRₕ</td>
<td>23</td>
<td>200±6</td>
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<td>0.92±0.04</td>
<td>0.91±0.02</td>
<td>31±2.0</td>
<td>0.7±0.1</td>
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<tr>
<td>DSₐ</td>
<td>18</td>
<td>203±4</td>
<td>209±5</td>
<td>0.95±0.06</td>
<td>0.99±0.04</td>
<td>28±3.0</td>
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<tr>
<td>DSₕ</td>
<td>20</td>
<td>207±6</td>
<td>211±6</td>
<td>0.90±0.04</td>
<td>0.94±0.02</td>
<td>33±4.0</td>
<td>0.7±0.1</td>
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</table>

Results of statistical analysis are presented in text. BUN, blood urea nitrogen concentration; Cr, plasma creatinine concentration; DRₐ, Dahl salt-resistant rat with a transplanted resistant kidney; DRₕ, Dahl salt-resistant rat with a transplanted sensitive kidney; DSₐ, Dahl salt-sensitive rat with a transplanted resistant kidney; DSₕ, Dahl salt-sensitive rat with a transplanted sensitive kidney.

Pressure was higher \((p<0.05)\) in DSₐ \((151±7\) mm Hg) than in DRₐ \((103±2\) mm Hg) (Figure 2 and Table 1). Second, mean arterial pressure did not differ significantly in DSₕ \((151±7\) mm Hg) and DRₕ \((145±5\) 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 DRₐ rats (151±7 mm Hg) and DRₕ rats (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).

Mortality Data

In the rats fed a low NaCl diet, the mortality during the 2 weeks after transplantation tended to be lower in DRₐ but did not differ significantly among the groups: DRₐ (2 of 12 or 16.7%), DRₕ (11 of 21 or 52.4%), DSₐ (11 of 22 or 50.0%), and DSₕ (6 of 17 or 35.3%). In the rats fed a high NaCl diet, the mortality also did not differ significantly among the groups: DRₐ (9 of 29 or 31.0%), DRₕ (17 of 40 or 42.5%), DSₐ (18 of 38 or 47.4%), and DSₕ (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%).

![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.](http://hyper.ahajournals.org/Downloadedfrom)
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, DS, and DRs). 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 R 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, DRs 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. 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, release or activation of a prohypertensive humoral substance, and deficiency of an antihypertensive factor possibly emanating from the renal medullary interstitial cells.

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 developed

<table>
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<th>Table 3. Body Weights, Arterial Pressure, and Renal Function in Uninephrectomized Dahl Rats Fed Low and High NaCl Diet</th>
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<td><strong>Group</strong></td>
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<tr>
<td>Low NaCl (0.4%) diet</td>
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<tr>
<td>DRs</td>
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<tr>
<td>DSs</td>
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<tr>
<td>High NaCl (8.0%) diet</td>
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<tr>
<td>DRs</td>
</tr>
<tr>
<td>DSs</td>
</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; DRs, Dahl salt-resistant rat that had undergone right nephrectomy; DSs, Dahl salt-sensitive rat that had undergone right nephrectomy.
significant NaCl-induced hypertension. Before concluding that this finding indicated an important role for extrarenal mechanisms in the DS rats, we considered alternative explanations for this observation.

One mechanism for the NaCl-induced hypertension in DS might be renal damage from the transplantation or rejection. This seems improbable for several reasons. Values for BUN and plasma creatinine concentration in DS 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 DR rats. Moreover, DR rats that underwent the same transplantation procedure as DS did not develop NaCl-induced hypertension. Therefore, NaCl-induced hypertension in DS 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 and DR 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) 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 hypertension 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 is as rapid or severe as in DS or DR rats. The point we wish to emphasize is not a quantitative comparison of the hypertension in DS, DR rats, and DR rats, but rather the fact that DS rats developed significant NaCl-induced hypertension (when compared with DR rats). It seems highly improbable that this important finding can be explained by selective mortality as the mortality rate in DS and DR rats was similar (31% in each group).

Dahl concluded from his observations that the kidney was the decisive influence in NaCl-induced hypertension. Our data indicate that extrarenal factors can also exert a decisive influence. At first glance, 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. Our findings during low NaCl diet are generally similar to Dahl's results and his conclusion that the kidney plays the primary role in determining chronic blood pressure level. Second, Dahl's limited observations in rats with renal transplantation fed high NaCl diet are not inconsistent with our conclusion. Dahl found that all four groups of rats with renal transplant (DR, DS, DS, and DS) developed hypertension during high NaCl diet. He concluded that this was caused by the combination of high NaCl diet and renal injury from the transplantation. 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 rats fed the high NaCl diet remained normotensive. The fact that the DR rats remained normotensive whereas DS rats developed hypertension 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 implicated, 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 rats (Tables 1 and 3). However, during high NaCl diet, the DS rats developed more hypertension than the DS rats with uninephrectomy (Tables 1 and 3). The kidneys from DS 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 uninephrectomy and DR rats even during high NaCl diet (Tables 1 and 3). These data indicate that the transplantation procedure per se has some prohypertensive 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 transplantation 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 rats develop NaCl-induced hypertension? In other words, does damage to the R kidney during transplantation promote hypertension or eliminate the normal antihypertensive influence of the R kidney? DR 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 cannot be explained by the transplantation procedure. It must reflect, instead, a role for extrarenal mechanisms. However, the precise contribution of extrarenal versus renal mechanisms to the NaCl-induced hypertension, independent of the effects of the transplantation.
tion procedure, cannot be stated from this or previous studies involving renal transplantation.

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

We gratefully acknowledge the excellent secretarial assistance of Sara Jedlicka and Nancy Davin and the technical assistance of Susan M. Staudt.

References

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**EFFECTS OF VARIOUS CALCIUM ANTAGONISTS**³

<table>
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<tr>
<th>RELAXES THE VESSELS</th>
<th>CARDENE</th>
<th>Nifedipine</th>
<th>Diltiazem</th>
<th>Verapamil</th>
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<td><strong>VASOSELECTIVITY</strong></td>
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<td>Blocks AV Conduction</td>
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<td>Nonvascular Smooth Muscle Side Effects</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+++*</td>
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Safe for Concomitant Use w/β-blockers: +++ + + +

Safety profiles are based on a scale from 0 to ++++, where 0 = least and ++++ = most.

*Particularly constipation in the elderly.

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†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.

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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. CARDENE 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).

Use in patients with impaired hepatic function: The drug should be used with caution in patients having impaired liver function or reduced hepatic blood flow. Patients with severe liver disease developed elevated blood levels (4-fold increase in AUC) and prolonged half-life (19 hours) of CARDENE.

Use in patients with impaired renal function: Mean plasma concentrations, AUC, and Cmax were approximately 2-fold higher in hypertensive mildly renally impaired patients treated with CARDENE than in healthy controls. Doses in these patients may need to be adjusted.

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

Digoxin: Some calcium blockers may increase the concentration of digitalis preparations in the blood. CARDENE usually does not alter the plasma levels of digoxin; however, serum digoxin levels should be evaluated after concomitant therapy with CARDENE is initiated.

Maisto: Co-administration of Maalox TC had no effect on CARDENE absorption.

Fentanyl Anesthesia: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with CARDENE, an increased volume of circulating fluids might be required if such an interaction were to occur.

Cyclosporine: Concomitant administration of nicardipine and cyclosporine results in elevated plasma cyclosporine levels. Plasma concentrations of cyclosporine should therefore be closely monitored, and its dosage reduced accordingly in patients treated with nicardipine.

When therapeutic concentrations of furosemide, propranolol, dipentolate, warfarin, quinidine, or naproxen were added to human plasma (in vitro), the plasma protein binding of CARDENE was not altered.

Pregnancy: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. CARDENE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is recommended that women who wish to breast-feed should not take this drug.

Pediatric Use: Safety and efficacy in patients under the age of 16 have not been established.

Use in the Elderly: Pharmacokinetic parameters did not differ between elderly hypertensive patients (≥65 years) and healthy controls after one week of CARDENE 20 mg TID. Plasma CARDENE concentrations in elderly hypertensive patients were similar to plasma concentrations in healthy young adult subjects when CARDENE was administered at doses of 10, 20 and 30 mg TID, suggesting that the pharmacokinetics of CARDENE are similar in young and elderly hypertensive patients. No significant differences in responses to CARDENE have been observed in elderly patients and the general adult population of patients who participated in clinical studies.

ADVERSE REACTIONS: In short-term (up to three months) studies 1,910 patients received CARDENE alone or in combination with other drugs. In these studies, adverse events were generally not serious but occasionally required dosage adjustment. Peak responses were not observed to be associated with adverse effects during clinical trials, but physician should be aware that adverse effects associated with decreases in blood pressure (tachycardia, hypotension, etc.) could occur around the time of the peak effect.

Angina: The most common adverse events include pedal edema and dizziness in about 7% of patients; headache, asthenia, flushing and increased angina in about 6%; palpitations in about 3%; and nausea and dyspepsia in about 2%. Adverse events occurring in about 1% of patients include dry mouth, somnolence, rash, tachycardia, myalgia, other edema and parasthesia. Sustained tachycardia, syncope, constipation, dyspnea, abnormal ECG, malaise, nervousness and tremor occurred in less than 1% of patients.

In addition, adverse events were observed which are not readily distinguishable from the natural history of the ath-erosclerotic vascular disease in these patients. Adverse events in this category each occurred in ≤0.4% of patients receiving CARDENE and included myocardial infarction, atrial fibrillation, excretory hypotension, pericarditis, heart block, cerebral ischemia and ventricular tachycardia. It is possible that some of these events were drug-related.

Hypertension: The most common adverse events include flushing in about 10% of patients; headache and pedal edema in about 8%; asthenia, palpitations and dizziness in about 4%; tachycardia in about 3%; nausea in about 2%; and somnolence in 1%. Dyspepsia, insomnia, malaise, other edema, abnormal dreams, dry mouth, nocturia, rash and vomiting occurred in less than 1% of patients.

Additionally, the following rare events have been reported: infection, allergic reaction, hypotension, postural hypoten- sion, styalic chest pain, peripheral vascular disorder, ven- tricular extrasystoles, ventricular tachycardia, sore throat, abnormal liver chemistries, arthralgia, hot flashes, vertigo, hyperkinesia, impotence, depression, confusion, anxiety, rhinitis, urticaria, tinnitus, abnormal vision, blurred vision, increased urinary frequency...

More detailed professional information available on request.

U.S. Patent No. 3,985,758

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