Primary Role of Renal Homografts in Setting Chronic Blood Pressure Levels in Rats

By Lewis K. Dahl and Martha Heine

ABSTRACT

The genotype of homograft kidneys plays the primary role in determining chronic blood pressure levels in two strains of rats with opposite genetically controlled propensities for hypertension. In hypertensive rats from the hypertension-prone (S) strain, a renal homograft from the same strain resulted in a slight rise in blood pressure to a level that was equivalent to that in appropriate uninephrectomized S controls. In contrast, a renal homograft from the hypertension-resistant (R) strain led to a sharp fall in blood pressure in hypertensive S recipients. Opposite results were found when the host came from the R strain: R homografts maintained the same low pressure as that seen in controls, whereas S homografts resulted in hypertension. We concluded that genetically controlled factors operating through the kidney can chronically modify the blood pressure up or down. The central role of the kidney in hypertension is thus further documented.

KEY WORDS

- genetic hypertension
- experimental hypertension
- salt
- heredity
- kidney transplant
- renal genotype

In two earlier papers (1, 2), we used interstrain renal transplants to study the influence of the kidney on blood pressure in two strains of rats that have opposite genetically determined propensities for hypertension. We found that the genotype of the renal homograft was more influential in determining the subsequent blood pressure development than was the genotype of the host rat, and we concluded that the kidneys of the hypertension-prone (S) strain had a greater hypertensinogenic and a lesser antihypertensive effect than did the kidneys of the hypertension-resistant (R) strain. In those studies, the course of blood pressure development was followed in initially normotensive young rats from both strains. In the present work, many of the rats from the S strain were allowed to become moderately hypertensive by consuming a high-salt (NaCl) chow for 4-5 weeks prior to the insertion of the renal homograft. We wanted to see whether the antihypertensive and hypertensinogenic qualities of the kidneys from these two strains would be demonstrable in the presence of hypertension.

Methods

Rats.—The rats came from one of two Sprague-Dawley strains that were originally established from a single strain on the basis of their different blood pressure responses to the same NaCl intake: one strain was resistant (R strain) and the other was sensitive (S strain) to the hypertensinogenic effects of NaCl (3, 4). Later we found that the two strains had similar disparate responses to most hypertensinogenic stimuli (5, 6).

Details on rat care and blood pressure measurement have appeared in earlier papers (7-12). Special chows made to order (Agway Inc., Country Foods Division, Syracuse, N. Y.) containing either 0.3% NaCl (low-salt chow) or 8% NaCl (high-salt chow) were fed ad libitum as specified. The low-salt chow contained adequate amounts of NaCl for normal growth and development. Tap water containing 0.5-0.7 mEq sodium/liter was allowed ad libitum. Rats fed the high-salt chow were given this diet for the first 4-5 weeks after weaning; they were then fed low-salt chow until the end of the experiment. Rats were observed as long as they remained in good health as evidenced primarily by maintenance of normal weight gain; however, observations on the rats with homografts ceased if their uninephrectomized controls became ill and vice versa. Survival ranged from 5 to 52 weeks with a median of 32 weeks. Only male rats were used. The rats were 8-9 weeks old at the time of surgery; at this time the S rats had been hypertensive about 3 weeks.

Kidney Transplantation.—The kidney transplantation procedure has been described in a previous paper (2). Briefly, it was a modification of the technique of Fisher and Lee (13) and of Lee (14). After the homograft had been inserted, the opposite (right) kidney was removed so that renal function was dependent solely on the single homograft kidney. Immunosuppressives and antibiotics were not used, but rejection was not a problem; failures were due to errors in technique and occurred approximately once in five operations, with failure being defined as death within 4 weeks after surgery.

Protocol.—Transplants were reciprocal as described earlier (1, 2). Four siblings from each of two litters were
used; one member from each litter was the host, one the donor, the third a uninephrectomized control, and the fourth an intact control. The uninephrectomized control and the host rat were of primary interest, and death or illness of either one was considered the end of the observation period for that pair. The intact control was essentially a control on its uninephrectomized sibling and proved unnecessary.

Systolic blood pressures were measured under light ether anesthesia by the microphonic method (7) prior to surgery and at 1-4-week intervals thereafter. Blood urea nitrogen was measured routinely as described previously (2). Weights were measured at each blood pressure determination. A weight loss in excess of 10 g was considered evidence of illness and only observations prior to such evidence were used in our calculations. Statistical comparisons between means were made by analysis of variance; data with \( P \) values < 0.05 were considered significant, and all \( P \) values < 0.01 were assigned that nominal value. The following symbols are used to identify the rats: "R" or "S" identifies the strain of the recipient, "r" or "s" denotes the strain of the donor, and "uni" indicates a control right uninephrectomized rat with its left kidney intact. Therefore, R_r, R_r, S_r, and S_s indicate the combinations of recipient and donor in this study, and R_uni and S_uni indicate the uninephrectomized controls.

The following questions were asked. (1) Would S rats with various degrees of hypertension that received a renal homograft from normotensive R rats have significantly lower blood pressures than their uninephrectomized sibling controls? (2) Would the opposite hold true, namely, would R rats with normal blood pressure that received a renal homograft from hypertensive S rats have significantly higher blood pressures than their uninephrectomized sibling controls?

**Results**

There were ten S_r rats; the recipient S rats had an average blood pressure of 167.8 ± 3.13 (SE) mm Hg prior to surgery, whereas the rats from which the donor R kidney came averaged 107.2 ± 3.54 mm Hg. The average pressure of the S_r rats was 122.8 ± 2.77 mm Hg at a median of 17 weeks after surgery. This pressure level contrasted with that of the uninephrectomized sibling S controls who averaged 186.0 ± 13.61 mm Hg at the same times \( P < 0.01 \) (Fig. 1).

The 12 R_r rats were derived from recipient R rats with an average blood pressure of 115.5 ± 2.55 mm Hg and S donor rats with an average blood pressure of 146.8 ± 7.15 mm Hg prior to surgery. Postoperatively, at a median of 24 weeks, the R_r rats averaged 155.0 ± 3.88 mm Hg and their uninephrectomized sibling controls averaged 128.1 ± 3.88 mm Hg \( P < 0.01 \) (Fig. 2).

The ten S_s rats originated from S donors with an average blood pressure of 142.4 ± 6.47 mm Hg and S recipients with an average blood pressure of 159.4 ± 1.88 mm Hg. The average pressure of the S_s rats at a median of 10 weeks after surgery was 166.8 ± 11.31 mm Hg compared with an average blood pressure of 167.4 ± 11.06 mm Hg for their uninephrectomized controls \( P > 0.05 \).

The 12 R_r rats came from R donors with an average blood pressure of 111.2 ± 2.55 mm Hg and R recipients with an average blood pressure of 147.5 ± 3.32 mm Hg. At a median of 30 weeks after surgery, the R_r homograft rats averaged 132.1 ± 3.92 mm Hg at a time when their uninephrectomized controls averaged 132.4 ± 3.61 mm Hg \( P > 0.05 \).

Among the rats with homografts, azotemia, defined as a blood urea nitrogen level of more than 50 mg/100 ml blood, occurred in five rats in the R_r group (53, 90, 78, 54, and 59 mg/100 ml blood), but...
Summary of Blood Pressures in Homograft and Control Rats

<table>
<thead>
<tr>
<th>Donor</th>
<th>BP* (mm Hg)</th>
<th>Recipient</th>
<th>BP* (mm Hg)</th>
<th>Homograft</th>
<th>BUN (mg/100 ml)</th>
<th>BP† (mm Hg)</th>
<th>Weeks postop.</th>
<th>Control</th>
<th>BUN (mg/100 ml)</th>
<th>BP† (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S (12)</td>
<td>146.8 ± 1.15</td>
<td>R (12)</td>
<td>115.5 ± 2.55</td>
<td>R (12)</td>
<td>55 ± 4.7</td>
<td>155.0 ± 4.80</td>
<td>24</td>
<td>R (12)</td>
<td>28 ± 2.3</td>
<td>128.1 ± 3.88</td>
</tr>
<tr>
<td>R (10)</td>
<td>107.2 ± 3.54</td>
<td>S (10)</td>
<td>167.8 ± 3.13</td>
<td>S (10)</td>
<td>33 ± 2.4</td>
<td>122.8 ± 2.77</td>
<td>17</td>
<td>S (10)</td>
<td>47 ± 3.3</td>
<td>186.0 ± 13.61</td>
</tr>
<tr>
<td>S (10)</td>
<td>142.2 ± 4.47</td>
<td>S (10)</td>
<td>159.4 ± 1.88</td>
<td>S (10)</td>
<td>41 ± 2.5</td>
<td>166.8 ± 11.31</td>
<td>10</td>
<td>S (10)</td>
<td>39 ± 5.9</td>
<td>167.4 ± 11.06</td>
</tr>
<tr>
<td>R (12)</td>
<td>111.2 ± 2.55</td>
<td>R (12)</td>
<td>107.5 ± 4.32</td>
<td>R (12)</td>
<td>31 ± 1.7</td>
<td>132.1 ± 3.92</td>
<td>30</td>
<td>R (12)</td>
<td>30 ± 1.9</td>
<td>132.4 ± 3.61</td>
</tr>
</tbody>
</table>

Weeks postop. = median number of weeks after surgery for homograft and control rats. All other values are means ± SE n = number of rats in the group. BP = blood pressure, and BUN = blood urea nitrogen.

* Systolic blood pressure immediately prior to surgery.
† Systolic blood pressure immediately prior to death.

Discussion

This study extends and strengthens the conclusions derived from our earlier work (1, 2) with renal homografts. There were four cases of azotemia in the S rat and R groups. There were no cases of azotemia in the S rats with a single R kidney (R, S, and R,). Weights of rats with a homograft and their respective controls were similar (∆P < 0.05) and therefore were not discussed further.

Table 1

Effect of the genotype of the renal homograft on chronic blood pressure levels at a median time of 24 weeks after surgery. Data are for all rats with a renal homograft (R). The mean blood pressure ± SE indicated for each group.

Circulation Research, Vol. 36, June 1975
opposite predispositions for developing hypertension. Depending on the genotype of the renal homograft, blood pressure can be chronically raised or lowered. Although it might be unwarranted to discount entirely the role of the host genotype, the kidney genotype appears to play the dominant role in setting chronic blood pressure levels. When for instance, rats from the hypertension-prone (S) strain are allowed to develop moderate hypertension from salt, replacement of both host kidneys by a single R homograft results in a significant chronic lowering of blood pressure: at similar times after surgery the average systolic blood pressure of S homograft rats is ~60 mm Hg less than that of their sibling S controls. By contrast, if an S donor is used, the resulting S rat shows no fall in blood pressure but instead a slight rise; in fact, such S rats and their uninephrectomized S controls have almost identical blood pressures of approximately 167 mm Hg. The homograft per se, therefore, does not induce a fall in blood pressure, a conceivable possibility from the results with the S homografts.

The R, combination results in opposite findings: R rats that are normotensive before surgery have average blood pressures after implantation of a single S hypertensive homograft kidney that are chronically 27 mm Hg higher than those in appropriate R controls at similar times after surgery. But if instead of an S donor, an R donor is used, the resulting R combinations have identical blood pressures with their R uninephrectomized controls. The homograft operation per se does not lead to a rise in blood pressure just as it does not lead to a fall in blood pressure. Any change in blood pressure induced in these homograft rats appears to be tied directly to the genotype of the renal transplant.

It seems reasonable to conclude that genetically controlled factors acting through the kidney can chronically modify the blood pressure up or down. Our studies with parabiosis between the two strains (15-17) have suggested indirectly that a humoral factor from the S kidney (or requiring the presence of the S kidney) can elevate blood pressure in a parabiont partner. Two later studies with renal homografts (1, 2) have led more directly to the conclusion that among normotensive rats from these strains the blood pressure can be directed to hypertensive levels or maintained at normotensive levels, depending on whether an S or an R genotype renal homograft is the sole source of renal function. The present study indicates that elevated blood pressures can be reduced to normal levels by a normotensive R kidney in a hypertensive S rat and that a hypertensive S homograft can raise the blood pressure of a normotensive R host.

In related studies with these two strains of rats, Tobian et al. (18) and Tobian (19) followed for 5 days the effect of renal homografts from the two strains on the blood pressure of rats with renal hypertension: kidneys from the S rats had less antihypertensive capacity than did kidneys from the R rats. This observation is compatible with our observations, but we now think that S kidneys have a greater capacity for raising blood pressure as well as a lesser capacity for lowering it compared with R kidneys.

The role of the kidneys in hypertension has been a subject of discussion since the time of Richard Bright and the subject of experiments for much of the twentieth century. The importance of the kidneys in controlling blood pressure has been reemphasized in a series of papers utilizing systems analysis by Guyton and his collaborators (20). It would not be helpful to the present thesis to detail the numerous factors outlined by these workers which modify chronic arterial blood pressure levels. The important point is that the central role of the kidneys in hypertension is documented in a series of elegant mathematical analyses combined with appropriate deductions based on experiments.

It perhaps is not surprising, therefore, that our work should point to the primary role of the kidneys in determining chronic blood pressure levels. The unique aspect of our studies is the finding that genetic determinants are involved in setting these blood pressure levels, i.e., in determining whether hypertension will develop; these genetic determinants clearly involve renal function. Nothing in this work suggests what aspect of renal function(s) is under genetic control. As we have pointed out earlier (2), the work of Muirhead et al. (21), Muehrcke et al. (22), and Tobian et al. (23) suggests the possibility that the antihypertensive capacity of the renal medulla differs in the two strains. We have no evidence at present either to support or refute involvement of the medulla in these rats, however.

**References**

4. Dahl LK, Heine M, Tassinari L: Effects of chronic excess salt ingestion: Evidence that genetic factors play an
18. TOBIAN L, COFFEY K, McCREA P, DAHL LK: Comparison of the antihypertensive potency of kidneys from one strain of rats susceptible to salt hypertension and kidneys from another strain resistant to it (abstr). J Clin Invest 45:1080, 1966
Primary role of renal homografts in setting chronic blood pressure levels in rats.

L K Dahl and M Heine

doi: 10.1161/01.RES.36.6.692

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1975 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/36/6/692

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/