Genetic Influence of the Kidneys on Blood Pressure

EVIDENCE FROM CHRONIC RENAL HOMOGRAFTS IN RATS WITH OPPOSITE PREDISPOSITIONS TO HYPERTENSION

By Lewis K. Dahl, Martha Heine, and Keith Thompson

ABSTRACT

In two strains of rats with opposite genetic propensities for hypertension, interstrain renal transplants chronically modified the blood pressure of the recipients. The blood pressure of rats with these renal homografts was largely determined by the genotype of the donor kidney rather than by the genotype of the recipient. Kidneys from the hypertension-resistant (R) rats generally had an antihypertensive effect, and kidneys from the hypertension-prone (S) rats had a prohypertensive effect. These effects on blood pressure were most clear-cut in rats maintained on a low-sodium diet, but they were still evident in a modified form in rats on a high-sodium diet. Results from this study and from earlier studies suggest that kidneys from S rats have a greater hypertensinogenic and a smaller antihypertensive capacity than do kidneys from R rats. Therefore the influence of the kidney on blood pressure appears to have genetic determinants. If this finding is applicable to man, it would help to explain the well-established but anomalous observation that one of two individuals who apparently have similar renal disorders can have hypertension when the other does not.

KEY WORDS

experimental hypertension hypertension-resistant rat hypertension-prone rat salt heredity kidney transplant

Bright (1) first correlated left ventricular hypertrophy with contracted kidneys and thereby initiated the concept of renal involvement in hypertension. A century later, Goldblatt et al. (2, 3) demonstrated an antihypertensive function of the kidney by showing that transient or mild hypertension induced in dogs by unilateral renal artery constriction could be converted to permanent, severe hypertension by either constriction of the renal artery or excision of the kidney on the contralateral side. Early work suggesting a protective action of the normal kidney has been reviewed by Braun-Menéndez et al. (4). Recently, Muirhead et al. (5) have reviewed and extended the evidence that the kidney, in particular the renal medulla, has an antihypertensive function.

Our studies on experimental hypertension have been done primarily with two unique strains of rats that have opposite genetic predispositions to hypertension. Using the technique of parabiosis between rats from these strains workers in our laboratory have indirectly shown that the kidneys play an important, genetically determined role in the development or the lack of development of hypertension after exposure to any one of several noxious stimuli commonly used to invoke experimental hypertension (6–8). The present study represents a natural extension of this earlier work; however, instead of developing more indirect evidence, we approached the problem directly. The most straightforward method for validating the genetically determined role of the kidneys in blood pressure regulation is to transplant kidneys between rats of the two strains and follow their blood pressures chronically. The present report summarizes a study in which rats were observed for 4–64 weeks after the dependence of renal function on a single homograft kidney had been established.

Methods

RATS

All of the rats belonged to one of two strains: one strain (R) was resistant to the effects of various noxious stimuli on blood pressure and the other (S) was sensitive to these stimuli. The two strains were derived from the same Sprague-Dawley rats by selective inbreeding with separation originally based on the sharply different blood pressure responses to a high-sodium intake (9, 10). It was found subsequently (7, 11,12) that these disparate blood pressure responses were not unique to a sodium stimulus but rather were indicative of similar opposite reactions to hypertensinogenic stimuli generally. This finding suggested that in these rats the develop-
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The transplant technique was a modification of the method of Fisher and Lee (16) and Lee (17). However, the rat's left kidney instead of its right kidney was replaced with the transplant, and the ureters were connected by end-to-end anastomosis instead of a bladder cuff. Surgery was done under ether anesthesia; a microscope (Cycloptic stereoscopic MT1) with an electric focus adjuster and instruments suitable for microvascular surgery were used (16, 17). The donor was prepared by freeing the left kidney, the renal artery and vein with adjacent segments of the aorta, the inferior vena cava, and the ureter from surrounding tissues with blood and urine flow left temporarily intact. Next, the recipient was similarly prepared; the donor remained under anesthesia. While the donor kidney was still in situ, its blood flow was interrupted, and it was gently flushed with cold saline (2-4°C) through the renal artery via the aortic stump until the effluent in the renal vein was clear, usually about 2 ml of saline was required. The homograft was then removed from the donor and immersed in cold saline (2-4°C) during the few minutes required for completing the removal of the recipient's left kidney.

A segment of the donor's aorta extending about 5 mm above and below the origin of the attached left renal artery was included in the homograft. The distal end of this aortic segment was tied off, and the proximal end was attached to the recipient's aorta through a 2-mm linear incision just below the origin of the left renal artery. The renal vein homograft included an oval cuff of the inferior vena cava about 3 mm long which was sewn into the recipient's inferior vena cava at the same level as the aortic graft. Continuous sutures were made for both anastomoses with monofilament 8-0 nylon attached to a 3/8-circle taper needle (TE-11 Atraumatic). Immediately after completion of the venous anastomosis, the clamp on the aorta and inferior vena cava was released and blood flow was restored. This procedure ordinarily was completed within a few minutes as evidenced by the return of normal color to the kidney. The total time of renal ischemia was 40-60 minutes, during which time the kidney was covered with gauze saturated by a continuous ice-cold saline drip. Urine formation often occurred before ureteral anastomosis between the homograft and the recipient had been completed. This ureteral anastomosis was made by inserting an 8-mm segment of silicone elastic tubing (Vivosil, 0.014 inches, i.d.) between the two cut ends, which were later united with one suture of the same nylon used on the vessels. The recipient's remaining (right) kidney was removed only after circulation to the homograft had been clearly established and oozing had ceased. A tissue adhesive (isobutyl 2-cyanoacrylate) was frequently used to stanch an oozing vascular anastomosis.

Clean but not sterile technique was used without either antibiotics or immunosuppressives. Other investigators (18, 19) have observed that with some combinations of rat strains renal homografts are accepted even when skin grafts are rejected. Since our two strains were both derived from the same original Sprague-Dawley parents, it is not surprising that the renal homografts were accepted. Reciprocal renal homografts between members of the spontaneously hypertensive rat (SHR) strain and our two rat strains uniformly resulted in acute rejection after 7-10 days. All rats were kept for 4 weeks postoperatively on the same low-sodium chow they had received since weaning.

**Table 1**

<table>
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<tr>
<th>Reciprocal Transplantation Protocol</th>
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<td><strong>Controls</strong></td>
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<tr>
<td><strong>Donor</strong></td>
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<tr>
<td>Litter A</td>
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<td>Litter B</td>
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1 We are indebted to Dr. A. I. Daniller of Montefiore Hospital and Medical Center, Bronx, N. Y., for teaching us this technique.

2 We thank Dr. George Jansen of Ethicon, Inc., Somerville, N. J., for the generous supplies of isobutyl 2-cyanoacrylate used in these studies.
velop mild elevations even on low-sodium diets (6). In these experiments, however, the important comparisons were those between sib 2 and sib 3, and sib 4 proved to be needless. Therefore, although the data on sib 4 were analyzed completely, they have not been included in this paper.

When two sets of four siblings were not simultaneously available, only a single transplant was made, and the donor always came from another litter. Using the nomenclature described above for litters, such an operation would involve only sibs 2A, 3A, 4A, and sib 1B.

The following symbols were used to describe the rats: R or S identifies the strain of the recipient, r or s identifies the strain of the donor, uni indicates a right uninephrectomized rat with the left kidney intact. Thus, Rr, Rs, Ss, and Sr indicate the four possible combinations of recipient and donor, and Runi and Suni indicate uninephrectomized controls.

Systolic blood pressures were measured under light ether anesthesia by the microphonic method (13) for all the rats involved (recipient, donor, and controls) prior to surgery and at 1–4-week intervals thereafter. An average of four readings was used for each measurement, although the variation among them was usually insignificant. Blood urea nitrogen was measured routinely at the end of the fourth postoperative week, every 2 months thereafter, and at death. Blood was obtained by nicking the tail at the end of the blood pressure measurement when the rat was still lightly anesthetized; blood urea nitrogen was determined with an autoanalyzer using 0.2 ml of plasma. Weights were measured at each blood pressure determination. Either of two criteria was used as an index of chronic illness: a permanent weight loss in excess of 10 g from any previous maximum (rats sometimes lost in excess of 10 g due to a transient intercurrent illness; after recovering, normal weight gain followed and, therefore, the rat was not considered to have been chronically ill) (20) or a blood urea nitrogen in excess of 50 mg/100 ml plasma. If either of these conditions was observed, blood pressure data collected only prior to its emergence were included in the statistical analyses.

Statistical comparisons among means were made by analysis of variance with special computer programs. Data with P values < 0.05 were considered significant, and P values < 0.01 were assigned that nominal value.

**Experiment 1:** Influence of Renal Homografts on the Blood Pressure of Rats Maintained on Low-Sodium Diet. — This experiment attempted to answer the following question. Would the genotype of the donor kidney have a greater influence on the blood pressure than the genotype of the recipient, unmodified by the hypertensinogenic effects of added NaCl? Among the 144 rats that received homografts (41 Rr, 37 Rs, 38 Sr, and 28 Ss), 115 (34 Rr, 28 Rs, 30 Sr, and 23 Ss) survived in good health on the low-sodium diet for at least 4 weeks; at this time 28 rats were removed with their controls for experiment 2, and observations were continued on the remaining 87 rats and their controls. The 1-month inter-

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val between operation and addition of sodium to the regimen of some rats was assumed to allow sufficient time for manifestation of renal failure due to rejection in the absence of immunosuppressives and technical failures.

**Experiment 2:** Influence of Renal Homografts on the Blood Pressure of Rats Started on High-Sodium Intake 1 Month after Surgery. — This experiment attempted to answer the following question. Would a high-sodium intake modify the influence of renal genotype on blood pressure observed in experiment 1? Experiment 2 was similar to experiment 1 except that it included the effect of added NaCl on 28 rats with renal homografts (8 Rr, 9 Rs, 6 Ss, and 5 Sr) and their controls.

**Results**

**EXPERIMENT 1**

The time (weeks) at which half of the rats were alive and in good health was used as one index of survival. For the S rats in all three groups (Ss, Sr, and Suni) this time was 24 weeks, and for the three groups of R rats it was 30–32 weeks (Fig. 1). This
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The difference is compatible with our extensive experience (unpublished observations) with these two strains, i.e., adult R rats generally survive any given regimen somewhat better than do adult S rats. The present results suggest that, in the rats that survived at least four weeks postoperatively, the homograft made no significant contribution to mortality.

Renal failure (Table 2) arbitrarily defined as a single blood urea nitrogen in excess of 50 mg/100 ml plasma at any time during the course of the experiment was observed in 17 of the 87 rats with homografts (3 Rs, 10 Rs, 2 Ss, and 2 Sr) and in 9 of the 87 uninephrectomized controls (3 R and 6 S). As indicated earlier, blood urea nitrogen was measured initially 4 weeks postoperatively and thereafter at 8-week intervals unless a rat was killed earlier because of patent terminal illness. Only four such elevations in blood urea nitrogen had occurred by the twentieth postoperative week (Table 2), at which time the patterns of blood pressure response shown in Figure 1 had been well established. Neither in these experiments nor in previous ones (15) has nitrogen retention been correlated with blood pressure levels.

Figure 1 shows the cumulative blood pressure measurements of the recipient rats and their uninephrectomized controls at biweekly intervals from the fourth week through the twenty-fourth week and every 4 weeks thereafter. The actual numerical data on blood pressure and survival rates summarized in Table 2 are abstracted from a more detailed analysis but accurately reflect the course of events. Note that cumulative pressures carried forward into subsequent averages and that the last pressure was recorded when the rat was in good health (20). No data are included on any recipient rat that failed to survive 4 weeks postoperatively.

The data in Figure 1 indicate that the blood pressure levels among the rats on low-sodium intake fall into two ranges averaging about 160 and 130 mm Hg; rats with a single S kidney had higher pressures (Ss = Rs = Suni, P > 0.05), and rats with a single R kidney had lower pressures (Sr = R = Sunir, P > 0.05). In both S and R recipients, those given a homograft from an S rat had significantly higher average blood pressures than those with a homograft from an R rat (Rs > R and Ss > Sr, P < 0.01). In contrast, in both S and R recipients given homografts from only one strain, mean blood pressure was similar (Rs = Suni and Sr = Ss, P > 0.05). It was not surprising that the blood pressure of Suni rats was greater than that of Sunir rats since the S rats generally had higher average blood pressures than did the R rats even if the R rats were on low-sodium intake (7, 9, 12). These results suggest that the genotype of the kidney was much more influential in determining chronic blood pressure levels than was the genotype of the recipient.

Table 2

<table>
<thead>
<tr>
<th>Weeks post-</th>
<th>Homograft</th>
<th>Blood urea nitrogen (mg/100 ml plasma)</th>
<th>Control</th>
<th>Blood urea nitrogen (mg/100 ml plasma)</th>
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<tr>
<td>14</td>
<td>R</td>
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FIGURE 2

Effect of renal homografts from S and R rats on the blood pressure (BP) of the recipients. All rats were switched from a low-sodium diet to a high-sodium diet 4 weeks postoperatively. See text for details and abbreviations. R, > R, at 6, 8, 10, and 12 weeks (P < 0.01) and at 14, 16, and 20 weeks (P < 0.05); Rs > Sr at 4, 6, and 10 weeks (P < 0.01) and at 12 weeks (P < 0.05); Sr > Sr at 4 and 8 weeks (P < 0.05) and at 6 and 10 weeks (P < 0.01); SUni > Runj at 6-20 weeks (P < 0.01); R, = Sr and R, = Sr at 6-16 weeks (P > 0.05).

kidney (8 R, 6 S, and 16 R,uni), survival was longer; more than half of the rats (5 R, 4 S, and 10 R,uni) were still alive at the sixteenth week. Of the original 55 rats in experiment 2, only 5 (2 R, and 3 R,uni) were in the study by the twenty-fourth week. This experience was somewhat different from that in experiment 1 because with all the rats on the low-sodium diet the recipient genotype seemed more important than did the donor genotype in determining longevity. By contrast, in the rats on the high-sodium diet (experiment 2) the donor’s genotype rather than the recipient’s genotype may have played the more dominant role in survival.

Renal failure (blood urea nitrogen > 50 mg/100 ml plasma) was observed in only two rats in this series: one S, rat at 12 weeks and one R,uni rat at 20 weeks (blood urea nitrogen 136 and 87 mg/100 ml plasma, respectively). As mentioned earlier, blood urea nitrogen was first measured at the end of the fourth postoperative week when all the rats went on a high-sodium diet, and generally it was not measured again until the twelfth week. Fifteen rats died between the fourth and twelfth weeks and, since blood urea nitrogen was not measured, it may have been elevated in some of these rats. These 15 deaths were approximately evenly divided: 8 uninephrectomized controls (3 R,uni, 5 S,uni) and 7 rats with homografts (3 R, 4 S,) died. Therefore, even if the unlikely assumption is made that all 15 died with elevated blood urea nitrogen, the rats with homografts fared at least as well as did the rats with a single kidney of their own.

The blood pressure responses of these groups of rats on the high-sodium diet are summarized in Figure 2. Comparison of Figures 1 and 2 shows a considerable difference in the average response for five of the six groups depending on whether sodium intake was low or high. Only with the R,uni controls was the effect of sodium negligible; the other five groups showed significant elevations in pressure after 2-4 weeks on the high-sodium diet. Nonetheless, the renal homografts from R rats had some moderating influence on blood pressure; no significant differences (P > 0.05) in average blood pressure were seen at the end of the fourth postoperative week just before the high-sodium diet was begun. However, from the sixth week through the twentieth week, the blood pressure of the R, rats was less than that of the R, rats (P < 0.05-0.01) and, from the sixth week through the tenth week, the blood pressure of the S, rats was less than that of the S, rats (P < 0.05-0.01). Predictably, the blood pressure of S,uni rats was greater than that of R,uni rats (P < 0.01).

Soon after the high-sodium diet was started at the end of the fourth postoperative week, elevated pressures began to develop in most rats regardless of the strain of the recipient or the donor. The development of hypertension was not due simply to the combined effect of the high-sodium diet and a single kidney, because the R,uni controls developed only mild elevations (144 mm Hg) on the high-sodium diet.

Discussion

These direct observations strengthen earlier conclusions derived indirectly: genetically controlled renal factors are critical determinants of the opposite predispositions for hypertension shown by these two strains of rats. The results of the earlier
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studies (6–8) may be briefly summarized as follows. In the S rats on a low-sodium diet, uninephrectomy alone induced mild hypertension, and unilateral renal artery constriction with the contralateral kidney intact caused severe hypertension. Unilateral renal artery constriction and contralateral nephrectomy enhanced the rate at which hypertension developed compared with the rate after renal artery constriction alone, but the final blood pressure levels reached were similar with the two techniques. However, in R rats, uninephrectomy or unilateral renal artery constriction had little or no effect on blood pressure. But, when R rats underwent unilateral renal artery compression and contralateral nephrectomy, severe hypertension that was comparable to that in similarly treated S rats resulted. Such studies strongly suggested that the protective action of intact renal tissue against hypertension was genetically controlled.

Other studies performed with the technique of parabiosis also suggested genetically controlled renal influences on blood pressure. This influence was first observed (6) after rats, one from each strain, were united in parabiosis and then placed on a high-sodium diet. Under these conditions, the reaction pattern to sodium ingestion changed, i.e., the R rat developed significant hypertension prior to its S partner. When unilateral renal artery constriction and contralateral nephrectomy (7) were performed on one member of a parabiotic pair, hypertension was induced in the operated rat and significant hypertension developed in the intact partner if the operated rat belonged to the S strain. In the third study (8), after the rats from the two strains were joined in parabiosis, one rat was nephrectomized. Renoprival hypertension was mild when such pairs received a special sodium-free diet compared with that when they received a high-sodium diet. In both cases, however, renoprival hypertension in S rats failed to induce high blood pressure in their intact partners. Renoprival hypertension thereby differed from the sodium-induced and renal hypertension in S rats. All of these experiments with parabiosis together indicated that a hypertensinogenic agent was transmitted across the parabiosis junction and that this hypertensinogenic agent was produced by the kidney of an S rat or required the functioning of the kidney from an S rat for its effect.

From these experiments it has been suggested "... that the kidneys of the hypertension-resistant (R) strain have an antihypertensive capacity, whereas those from the hypertension-prone (S) strain have a hypertension-promoting capacity" (21). This statement could be interpreted as meaning that kidneys from R rats lacked all hypertensinogenic potential and that kidneys from S rats lacked all antihypertensive ability. This interpretation was not intended; rather the statement meant that kidneys "... in the R strain have a more powerful antihypertensive influence, whereas those of the S strain are more hypertensinogenic" [9].) Therefore, it was postulated that the kidneys had a "... decisive, genetically determined, influence in the development of both salt and renal hypertension" (21). It was further proposed that this influence probably would hold true for hypertension generally.

In the present study, in rats maintained on the low-sodium diets, the R rats had kidneys that retarded the development of hypertension when they were transplanted to S rats. Conversely, kidneys from S rats promoted the development of hypertension in R rats. These effects were somewhat modified when similar rats were placed on a high-sodium diet in that most of the rats with homografts developed significant hypertension. Nonetheless homografts from R rats retarded the development of hypertension, although the effect was muted compared with that in rats on the low-sodium diet (experiment 1).

If the kidney is intimately involved in the control of blood pressure in these rats as experiment 1 suggests, it is not surprising that the rats with a single kidney from an S rat (R, S, S) developed hypertension, because intact S rats develop fulminating hypertension in response to NaCl alone (20) and this effect would be exaggerated in a rat with only one kidney. It was surprising, however, that hypertension developed in some of the R and the S rats, since the renal homografts came from the R strain that is generally resistant to the hypertensinogenic influence of NaCl. On the basis of our previous experience with R rats on a high-sodium diet, rats with a single kidney from an R rat fed NaCl should have developed a mild blood pressure elevation comparable to that actually observed in this experiment in the uninephrectomized control R rats.

Although the effect of the high-sodium diet in rats with a homograft from an R rat cannot be definitely explained, the probable explanation is that the homografts suffered injury during or after operation (unpublished observation). Injury to the homograft may have resulted from tissue anoxia suffered at the time of operation when the renal
The homograft was without blood for 40–60 minutes, from subclinical rejection of the homograft, from chronically impaired renal blood flow due to constriction at the surgical anastomosis between the renal artery and the aorta, or from a combination of these conditions. It was further assumed from the results of experiment 1 that any such renal damage was insufficient by itself to cause hypertension but required the added noxious stimulus of the high-sodium diet to cause hypertension (experiment 2). Anoxic injury was explored in initially intact rats by clamping the left renal artery for 60 minutes and then releasing the clamp and removing the right kidney; during the succeeding months hypertension developed in some but not all of the R rats on the high-sodium diet but not in those on the low-sodium diet. Subclinical rejection was studied with renal autografts, i.e., the left kidney was removed and immediately reimplanted in the same rat, after which a right nephrectomy was performed. Some of these R rats subsequently developed hypertension on the high-sodium diet but not on the low-sodium diet. Chronically impaired renal blood flow was studied by measuring para-aminohippuric acid clearance and inulin clearance in rats with homografts and in their controls. No evidence was found to suggest impaired renal blood flow. Direct visualization of the anastomotic sites at the time of death did not indicate stenosis. Therefore, it was tentatively hypothesized that the combination of renal anoxic injury and high-sodium intake was sufficient to induce hypertension in unhypertensinogenized R rats. The fact that some R rats with autografts developed hypertension did not, however, entirely rule out the possibility that injury from subclinical rejection made some contribution to the development of hypertension in rats with homografts.

Tobian et al. (22) and Tobian (23) have reported results from some short-term studies with these two strains of rats which are compatible with the long-term results presented in the present paper. In a rat with renal hypertension induced by unilateral renal artery compression and contralateral nephrectomy, a kidney from either an R or an S rat was connected into the circulation and then the recipient’s remaining kidney was removed. The effect of the renal homograft on the blood pressure of the hypertensive rat was observed for 5 days. At this time, from an average pretreatment systolic pressure of approximately 200 mm Hg, the 23 rats with an R kidney averaged 111 mm Hg and the 36 rats with an S kidney averaged 137 mm Hg ($P = 0.002$). Therefore, the kidneys from the S rats had less antihypertensive potency than did those from the R rats.

The results of earlier experiments (6–9) combined with those of the present study have led to the conclusion that the kidneys of S rats probably have not only a smaller antihypertensive capacity but also a greater hypertensinogenic capacity compared with those of R rats. This conclusion represents no substantive disagreement with the previous studies (22, 23).

Neither this study nor the earlier studies have elucidated the mechanism(s) by which these effects are produced. The elegant studies of Muirhead et al. (5), Muehrcke et al. (24), and Tobian et al. (25, 26) suggest that the antihypertensive function of the renal medulla may differ in the two strains. We have reported that, as judged by juxtaglomerular granulation (27) and plasma and kidney levels (28), renin activities are significantly lower in S rats when rats from both strains are subjected to similar regimens. This finding indicates that renin activities are modified by genetic influences. Although we can offer no satisfactory mechanism to explain the effects on blood pressure, the constancy of these differences in renin activities suggests that the renin-angiotensin system may be involved in the disparate blood pressure responses manifested by the two strains.

Caution should be used in extrapolating data derived from rats to man. At the same time, it is unlikely that the present data derived from these genetically dissimilar rats are totally irrelevant to man. If the kidneys in man are under similar genetic influences, this finding would help to explain the well-established observation that one of two individuals who have apparently similar renal disorders can have hypertension when the other does not.

References


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