Genetic Influence of Renal Homografts on the Blood Pressure of Rats from Different Strains[1] (36566)

LEWIS K. DAHL, MARTHA HEINE, AND KEITH THOMPSON

Medical Department, Brookhaven National Laboratory, Upton, New York 11973

The well-established association between the kidneys and hypertension was first implied in the 19th century by Richard Bright, who related cardiac hypertrophy to renal disease (1). More recently, evidence has evolved indicating that the kidneys also have an antihypertensive function (2–4).

We have been studying experimental hypertension utilizing two unique strains of rats (5) derived from common Sprague-Dawley ancestors, and possessing opposite genetic predispositions to experimental hypertension. Their genetic separation originally was based on divergent blood pressure responses to ingested salt (NaCl). The hypertension-prone (sensitive or S) animals develop fatal hypertension from salt intakes to which hypertension-resistant (resistant or R) animals respond mildly, if at all. Five other methods, commonly used for inducing experimental hypertension were later found to evoke similarly disparate responses (5d–f). The genetic substratum was critical, therefore, in determining the efficacy of most insults commonly used to induce experimental hypertension. There is considerable circumstantial evidence which suggests that this also holds true for hypertension in man (5e, h).

Previous evidence (5f, 6a–c) had suggested that the kidneys of rats from these two strains may differ in that those in the R strain have a more powerful antihypertensive influence, whereas those of the S strain are more hypertensinogenic. A validation of these indirect observations would be obtained by transplanting kidneys *between* members of the two strains and determining their respective influences on blood pressure. This paper is the first report of such experiments.

The transplantation technique was that of Lee (7) as modified by Dr. A. I. Daniller.[2] It uses an operating microscope and surgical instruments appropriate to vascular microsurgery. The major modifications from those described by Lee are that (a) the left instead of the right kidney is replaced with a transplant and (b) the ureter is connected by end-to-end anastomosis instead of by a bladder cuff. The homograft is without blood flow for the 40–60 min required for the surgery during which time it is covered with gauze saturated by a continuous drip of ice-cold saline. The recipient's remaining (right) kidney is removed after the homograft reestablishes its blood flow, as evidenced by return of normal color—usually within a few minutes. Urine formation often begins in the homografts before their ureteral anastomoses have been completed. Immunosuppressives were not administered: in agreement with the observations of Salaman and of White and Hildemann (8a, b), acute rejection of the transplanted kidney was not a problem in this work. Males approximately 6 weeks old at the time of operation were used. To minimize genetic variation, 2 groups, each of 4 male sibs from different litters, were generally utilized for reciprocal transplants as follows:

	Donor	Recipient	Controls	
			Uninephrectomized	Intact
Litter A	Sib 1A	Sib 2A	Sib 3A	Sib 4A
Litter B	Sib 1B	Sib 2B	Sib 3B	Sib 4B

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[2] We thank Dr. Daniller, now at the Hospital for Sick Children, Toronto, Canada, for teaching us this technique.

Ordinarily, Sib 1A provided the renal transplant for Sib 2B, and Sib 1B for 2A, after which Sibs 1A and 1B were sacrificed. When two full sets of 4 male sibs were not available simultaneously, only a single transplant was made and Sibs 1A, 2B, 3B and 4B were not included but the donor rat always came from a different litter. Because the animal with a homograft (Sib 2) had only one kidney, a (right) uninephrectomized sib (Sib 3) served as its primary control. The intact sib (Sib 4) was, in effect, a control for this uninephrectomized sib. These double controls were considered necessary because in rats from the S strain, uninephrectomy alone elevates the blood pressure (5f) and intact rats from the S strain can gradually develop mild hypertension even on low salt intakes (5f, i).

Blood pressure was measured by a standard technique (5a) prior to operation, 4 weeks later, and then every 1 to 4 weeks depending upon the severity of hypertension. Blood urea nitrogen (BUN) was measured on each rat at the end of the 4th postoperative week and routinely at least every 2 months thereafter. Weights were recorded concomitantly with blood pressures. A weight loss in excess of 10 g from any previous maximum was used as evidence of illness (5 g) and therefore only blood pressure data collected prior to such loss were analyzed. Water and chow (0.4% NaCl) were allowed *ad libitum*. Animals with homografts were caged singly; their two controls, together.

Blood pressure comparisons were made among the following groups of animals:

1. R_r = R recipient with R homograft
2. R_s = R recipient with S homograft
3. S_r = S recipient with R homograft
4. S_s = S recipient with S homograft
5. R uni = uninephrectomized R control for R_r homograft
6. R uni = uninephrectomized R control for R_s homograft
7. S uni = uninephrectomized S control for S_r homograft
8. S uni = uninephrectomized S control for S_s homograft
9. R intact = intact R control for R_r homograft
10. R intact = intact R control for R_s homograft
11. S intact = intact S control for S_r homograft
12. S intact = intact S control for S_s homograft

Statistical comparisons between means were made with the Student-Newman-Keuls multiple range technique (9).

Of the 140 rats that received homografts, only data on the 113 animals that survived in good health (see weight loss, above) for at least 4 weeks following operation were analyzed. The average survival of these 113 was, in fact, slightly over 4 months and the maximum was 14 months.

The pertinent blood pressure data are summarized in Tables I and II. Table I shows that blood pressure was not significantly ($p > .05$) affected compared with uninephrectomized controls when the recipient animal and its renal homograft derived from the *same* strain. It was therefore concluded that the operation, *per se*, did not affect the blood pressure.

When recipient and homograft came from *different* strains, a significant ($p < .01$) effect on blood pressure was observed (Table II). Animals from the hypertension-resistant (R) strain with a renal homograft from the hypertension-prone (S) strain had ***higher*** pressures, whereas S rats with an R homograft had *lower* pressures, than their respective uninephrectomized controls (Tables I and II).

Among the 4 groups with homografts, there were two different levels of blood pressure response:

	BP (mm Hg)	
	1 month	4 months
R_s	143.4	157.6
S_s	143.4	154.6
S_r	126.4	130.6
R_r	130.6	128.1

These data suggest that the phenotypic response—blood pressure—was more influenced by the genotype of the renal homograft than by the genotype of the recipient.

Data on the concentration of blood urea nitrogen (BUN) have not been included in this report. Animals with R kidneys tended

TABLE I. Lack of Effect on BP when Recipient and Donor Kidney Came from the Same Strain (R_r or S_s).[a]

		BP (mm Hg; ± SE)					
		n	Preop	*n*	1 month postop	*n*	Av 4 months postop
R_r	Test	37	114.7 (1.96)	37	130.6 (1.47)	28	128.1 (2.39)
R (uni)	Control	44	115.7 (1.75)	44	127.5 (1.33)	33	130.5 (2.20)
R (intact)	Control	44	118.1 (1.75)	44	124.3 (1.35)	33	127.9 (2.20)
S_s	Test	23	121.1 (2.47)	23	143.4 (1.85)	17	154.6 (3.07)
S (uni)	Control	28	119.9 (2.19)	28	136.9 (1.67)	21	150.4 (2.76)
S (intact)	Control	28	123.4 (2.19)	28	138.7 (1.67)	20	158.6 (2.83)

[a] R_r = R recipient with R kidney homograft; S_s = S recipient with S kidney homograft; uni = uninephrectomized control; intact = intact. Animals with homografts that died within 1 month postoperatively were not included in calculating preoperative means; hence the difference between the number of test and control animals initially. At the end of 1 month 9 and 6 triplets (homograft, uninephrectomized, and intact animal) were removed from the R_r and S_s groups, respectively, and placed on high NaCl. Data on these, and subsequent, salt-fed rats with homografts will be included in a detailed report now in preparation. Any other differences in numbers was due to deaths between first and fourth month. Statistics: Blood pressure:

$$\left.\begin{array}{l}\text{Preop.}\\ \text{1 month}\\ \text{4 months}\end{array}\right\} \quad \left.\begin{array}{l}R_r = \text{R uni} = \text{R intact}\\ S_s = \text{S uni} = \text{S intact}\end{array}\right\} \quad p > .05.$$

to have slightly lower BUN values than comparable rats with S kidneys, whether intact, uninephrectomized or with a homograft. Uremia was not a frequent complication: only 10 of the 113 rats with homografts were found to have BUN in excess of 40 mg% at some time during the course of this study, in but 3 of which did it exceed 50 mg%. In any event, there was no correlation between an elevation in BUN and in blood pressure; nor was there a consistent difference in BUN concentration between animals with homografts and their respective uninephrectomized controls.

The direct observation that the chronic modification of blood pressure by renal homografts was more influenced by the genotype of the homograft than of the recipient is in line with earlier, indirect, observations on these rats. The findings here strengthen the probability that some of the difference in blood pressure response in these two strains of rats depends on genetically determined factors in the kidney (5f, 6a–c).

Summary. In two strains of rats with opposite genetic propensities to hypertension, the effect of renal transplants on the chronic blood pressure response has been studied. 113 rats survived an average of 4 months (range 1–14) after this procedure. Among animals maintained on a low NaCl diet, blood pressure, as compared with appropriate controls, was not significantly affected when the recipient animal and its renal homograft came from the same strain; however, animals from the hypertension-resistant strain with a renal homograft from the hypertension-prone strain had higher pressures whereas hypertension-prone rats with a homograft from the hypertension-resistant strain had lower pres-

TABLE II. Effect on BP when Recipient and Donor Kidney Came from Different Strains (R_s or S_r).[a]

		BP (mm Hg; ± SE)					
		n	Preop	n	1 month postop	n	Av 4 months postop
R_s	Test	23	107.5 (2.42)	23	143.4 (1.84)	9	157.6 (4.21)
R (uni)	Control	32	112.6 (2.05)	32	123.6 (1.56)	14	132.6 (3.38)
R (intact)	Control	32	115.1 (2.05)	32	121.9 (1.56)	14	132.9 (3.38)
S_r	Test	30	115.2 (2.12)	30	126.4 (1.61)	14	130.6 (3.38)
S (uni)	Control	36	116.7 (1.93)	36	138.6 (1.47)	17	152.4 (3.07)
S (intact)	Control	36	117.1 (1.93)	36	136.5 (1.47)	17	146.2 (3.07)

[a] See legend for Table I. R_s = R recipient with S kidney homograft; S_r = S recipient with R kidney homograft. At the end of 1 month, 9 and 8 triplets were removed from R_s and S_r groups, respectively, as described in legend for Table I. Statistics: Blood pressure:

Preop

$$\left.\begin{array}{l} R_s = R\text{ uni} = R\text{ intact} \\ S_r = S\text{ uni} = S\text{ intact} \end{array}\right\} \quad p > .05$$

1 month

$$\left.\begin{array}{l} R_s > R\text{ uni} \\ R_s > R\text{ intact} \end{array}\right\} \quad p < .01$$

$$\left.\begin{array}{l} S_r < S\text{ uni} \\ S_r < S\text{ intact} \end{array}\right\} \quad p < .01$$

4 months

$$\left.\begin{array}{l} R_s > R\text{ uni} \\ R_s > R\text{ intact} \end{array}\right\} \quad p < .01$$

$$\left.\begin{array}{l} S_r < S\text{ uni} \\ S_r < S\text{ intact} \end{array}\right\} \quad p < .01$$

sures than their respective controls. Thus, the phenotypic response—blood pressure—was more influenced by the genotype of the renal homograft than by the genotype of the recipient.

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