Inheritance of Salt-Dependent Hypertension in the Inbred Dahl Rat

Richard E. Abbott, David Schachter

Abstract The mode of inheritance of salt-dependent hypertension in the inbred Dahl salt-sensitive rat strain was examined by genetic crosses with the corresponding salt-resistant strain. The blood pressure responses to ingestion of a high NaCl (8%) diet defined three phenotypes: early onset (within 17 days) of systolic hypertension, defined as greater than or equal to 140 mm Hg, the parental salt-sensitive phenotype; late onset of systolic hypertension requiring 50 to 60 days in males and more than 200 days in females, characteristic of the F1 progeny; and normotension, less than 140 mm Hg, the parental salt-resistant phenotype. The frequencies of the phenotypes observed among 91 F2 progeny and 45 progeny of the backcross to parental salt-sensitive animals agree well with values predicted by a model in which two autosomal, unlinked, allelic loci, termed α and β, determine the inheritance. For F1 male progeny, the predicted frequencies of early-onset hypertension, late-onset hypertension, and normotension are 0.1875, 0.5625, and 0.25, respectively, and the corresponding observed frequencies were 0.156, 0.50, and 0.34 (χ²=0.48, P>.50). F1 progeny of reciprocal parental crosses were maintained on the 8% NaCl diet for 255 days. Male F1 rats developed systolic hypertension sooner than did females. From 60 to 200 days, the average blood pressure value within each group remained approximately stable; the male values exceeded those for females (P<.01); and the direction of the parental cross significantly influenced (P<.05) the levels in males and females, suggestive of genomic imprinting. (Hypertension. 1994;24:506-511.)

Key Words • rats, inbred strains • genetics • gender • genome

The phenotypic characteristics of genetically determined, salt-dependent hypertension in the Dahl rat strain have been widely studied and well summarized in periodic reviews.1,2 The mode of inheritance of the disorder, however, remains unclear. Knudsen et al3 examined F1, F2, and backcross progeny in a prodigious study of approximately 2000 outbred, Brookhaven, salt-sensitive (S) and salt-resistant (R) rats over a 6-year period. Focusing on the systolic blood pressure levels observed after rats had been 24 weeks on an 8% NaCl diet, the authors noted a broad, apparently unimodal distribution of values and concluded that the inheritance was polygenic and complex. The simplest model to account for the distribution of the blood pressure levels assumed two unlinked, autosomal, allelic loci. In males, the S alleles were assumed to contribute additively, so rats with 0 to 1, 2, or 3 to 4 such alleles should exhibit the salt-resistant, an intermediate, or the salt-sensitive blood pressure level, respectively. Females were postulated to be similar except for dominance of the R allele at one locus. While this study is an important contribution, it has a number of limitations. The mating of outbred, genetically inhomogeneous strains makes interpretation uncertain. Focus on the blood pressure levels at 24 weeks ignores the significance of earlier hypertensive responses and entails the complications of significant prior mortality and hypertensive tissue damage, which can secondarily affect blood pressure values. The need to maintain a relatively large rat colony for an extended time makes the experimental design quite expensive; perhaps for that reason, similar studies have not been reported by others. Finally, the proposed model did not account for the blood pressure levels of their female progeny of backcross matings to parental S animals.

This report describes mating experiments designed to overcome the foregoing limitations and to provide a more detailed and heuristic model of the mode of inheritance. Genetic crosses of the inbred S and R rat strains developed by Rapp and Dene2 were studied in our laboratory over the past 2 years. The F1, F2, and backcrosses to parental S progeny were placed as weanlings on an 8% NaCl diet, and the time to onset and the frequency of occurrence of systolic hypertension, defined as greater than or equal to 140 mm Hg in the unanesthetized rat, were determined. The observations led us to define two hypertensive phenotypes: early onset of hypertension occurs within 17 days of the start of the high salt diet in both males and females and is the parental S phenotype; late onset of hypertension is observed in F1 progeny and requires approximately 50 to 60 days in males and more than 200 days in females. The experimental data described below support the following working model of the mode of inheritance. Two autosomal, unlinked, allelic loci termed α and β control the inheritance of the S phenotype. The S alleles at the α locus (ie, αS) are recessive in both males and females. The S alleles at the β locus (ie, βS) are dominant in both males and females. Rats homozygous for the recessive αS allele and possessing at least one βS allele manifest the parental S phenotype of early onset of systolic hypertension when fed the 8% NaCl diet; males and females express this phenotype similarly.

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Rats not homozygous for the \( a_s \) allele and possessing at least one dominant \( B_s \) allele manifest the late-onset phenotype; expression occurs much sooner in males than in females.

### Methods

#### Animals

Inbred rats of the Rapp strains SS/Jr and SR/Jr (hereafter referred to as Dahl S and R, respectively) were obtained from Harlan Sprague Dawley or from matings in our approved animal care facility as indicated below. (In view of stock contaminations at Harlan Sprague Dawley in early 1992, it is important to note that all progenitor rats used were obtained before August 1991.) Parents for matings were fed a nutritionally complete rodent pellet diet (Purina #5001, Purina Mills) containing 0.4% NaCl plus water ad libitum. Progeny of the matings performed by the vendor or in our facility were placed on the same regimen at 21 days of age and housed in individual metabolic cages. At 28 days of age, the same diet containing 8.0% NaCl (high salt) was begun, and the body weights and systolic blood pressure levels were estimated periodically. All animal procedures were in accordance with our institutional guidelines.

#### Blood Pressure Estimations

Unanesthetized rats were prewarmed and their systolic blood pressure levels were estimated indirectly by tail plethysmography with a programmed electrosphygmomanometer (model PE-3000, Narco BioSystems). At least four or five readings obtained at 5-minute intervals were averaged for each determination. This method, rather than intra-arterial catheterization, was used because each rat was tested over a period of months, as described below. Environmental conditions for the tests were carefully controlled (same room, same tester, quiet environment, mild warming). The method was also validated by a biometric ANOVA of the blood pressure levels in \( F_1 \) and \( F_2 \) populations as described by Kurtz et al.\(^4\) The percentage of the variance owing to genetic compared with environmental factors (including "noise" resulting from the method of estimation) was calculated as (variance in \( F_2 \) progeny−variance in \( F_1 \) progeny)÷(variance in \( F_2 \)). After 17 and 32 days on the high salt diet, the values were 79% and 88%, respectively, and compared favorably with the value of 60% in the study of Kurtz et al.\(^4\)

#### Statistical Analysis

ANOVA of repeated measurements\(^5\) and \( \chi^2 \) analysis were applied.

### Results

#### Parental Strains

Groups of seven male and seven female inbred Dahl S rats were obtained as weanlings from Harlan Sprague Dawley and placed on the 8.0% NaCl diet at 28 days of age to monitor their blood pressure responses. The results are plotted in Fig 1, along with corresponding values for \( F_1 \) males and females (see below) and R strain males. A relatively rapid increase in systolic blood pressure occurred in all the parental S animals, and hypertensive levels (≥140 mm Hg) were observed uniformly by diet days 14 to 17. By contrast, blood pressure values of the \( F_1 \) progeny increased relatively gradually to approximately 120 mm Hg and remained normotensive throughout the observation period of 32 days. The hypertensive responses of the parental S strain males and females were similar; ANOVA indicated no significant difference in blood pressure owing to gender (F ratio, 0.91). From these results, we adopted an operational definition of the parental S phenotype as the development of systolic blood pressure levels greater than or equal to 140 mm Hg by day 17 in animals fed the 8% NaCl diet from 28 days of age. Inasmuch as this relatively early hypertensive response was not observed in the \( F_1 \) progeny, we postulated that it is inherited as a recessive trait expressed similarly in both males and females and is controlled by an autosomal allelic locus termed the \( a \) locus.

#### \( F_1 \) Progeny

Reciprocal matings of the parental strains, S dam×R sire (S×R) and R dam×S sire (R×S), were performed by Harlan Sprague Dawley, and groups of seven male and seven female \( F_1 \) progeny of each cross were supplied as weanlings. The animals were fed the 8% NaCl diet starting at 4 weeks of age, and systolic blood pressure values were determined up to 255 days. Figs 2 and 3 illustrate the values observed for progeny of the S×R and R×S crosses, respectively. In contrast to the
By diet day 255, hypertensive levels were recorded for the phenotype of late onset of salt-dependent hypertension, which exhibits no gender difference and develops similarly in males and females.

The values in Table 1 also indicate significant effects ($P<.05$) of the direction of the parental cross on the blood pressure levels in the 60- to 200-diet-day interval. F₁ males inheriting S genes from the father (RxS cross) had a mean value 9 mm Hg greater than that of F₁ males of the R×S cross. Conversely, F₁ females inheriting S genes from the father (R×S cross) had a mean value 10 mm Hg greater than that of females of the S×R cross. As a consequence, the mean male-female increment of 34 mm Hg in the S×R progeny was considerably greater than the corresponding increment of 15 mm Hg in the R×S progeny. The results indicate parental influences on the expression of the $\beta_a$ allele in F₁ progeny and demonstrate that the progeny of S×R crosses are particularly suited for exploration of the mechanisms underlying the gender differences.

### Working Model and Predictions

A working model was formulated to permit the calculation of predicted frequencies of each of the three phenotypic responses to the high salt diet: normotension, the parental R phenotype; early onset of hypertension, the parental S phenotype; and late onset of hypertension. Assuming that the \( a_s \) and \( \beta \) loci are nonlinked and the alleles assort independently, there are nine possible genotypes, as listed in Table 2. Also shown are the phenotypes expected for a model in which the phenotype of normotension requires $\beta_s\beta_s$, that of early onset of hypertension requires both $\alpha_s$ alleles plus at least one $\beta_a$ allele, and that of the late onset of hypertension requires at least one $\alpha_R$ plus one $\beta_a$ allele.

All nine genotypes shown in Table 2 are expected in the F₁ progeny resulting from matings of F₁ parents, i.e., $\alpha_s\alpha_s/\beta_s\beta_s \times a_R,a_s/\beta_s\beta_s$. Random assortment predicts the frequency distribution of the $\alpha$ alleles in the F₂ progeny as $\alpha_s\alpha_s(0.25)$, $\alpha_R\alpha_R(0.50)$, and $\alpha_R\alpha_s(0.25)$, and the same distribution holds for the $\beta$ alleles. Hence, the

### Table 1. Effects of Sex and Direction of Parental Cross on Systolic Blood Pressure in F₁ Progeny

<table>
<thead>
<tr>
<th>Direction of Cross (Dam×Sire)</th>
<th>Systolic Blood Pressure, mm Hg, mean±SEM</th>
<th>$F$ Ratio*</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>S×R</td>
<td>153±3</td>
<td>119±2</td>
<td>74.8</td>
</tr>
<tr>
<td>R×S</td>
<td>144±4</td>
<td>129±3</td>
<td>10.8</td>
</tr>
<tr>
<td>$F$ ratio†</td>
<td>5.14</td>
<td>6.75</td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td>&lt;.05</td>
<td>&lt;.05</td>
<td></td>
</tr>
</tbody>
</table>

$S$ indicates salt-sensitive strain; $R$, salt-resistant strain. Systolic blood pressure values shown are for seven rats of each gender fed an 8% NaCl diet for 4 weeks of age.

* $F$ ratio for the difference between males and females calculated by ANOVA of repeated measurements.

† $F$ ratio for the difference between S×R and R×S crosses calculated as above.
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### TABLE 2. Genotypes, Phenotypes, and Predicted Genotype Frequencies

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Predicted Phenotype</th>
<th>F₂</th>
<th>Backcross to S</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} )</td>
<td>Normotension</td>
<td>0.0625</td>
<td>0.25</td>
</tr>
<tr>
<td>( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} )</td>
<td>Early hypertension</td>
<td>0.0625</td>
<td>0.25</td>
</tr>
<tr>
<td>( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} )</td>
<td>Late hypertension</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} )</td>
<td>Late hypertension</td>
<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} )</td>
<td>Late hypertension</td>
<td>0.0625</td>
<td>0.25</td>
</tr>
<tr>
<td>( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} )</td>
<td>Normotension</td>
<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} )</td>
<td>Late hypertension</td>
<td>0.125</td>
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<td>( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} )</td>
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<td>( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} )</td>
<td>Early hypertension</td>
<td>0.125</td>
<td>0.25</td>
</tr>
</tbody>
</table>

S indicates salt-sensitive; R, salt-resistant. Genotypes corresponding to parental R, parental S, and \( F_1 \) respectively, are \( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} \), \( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} \), and \( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} \). Phenotypes are predicted from the working model: normotension, \( a_{\beta}a_{\beta} \); early-onset hypertension, \( a_{\alpha}a_{\beta}/a_{\beta}a_{\beta} \); late-onset hypertension, \( a_{\alpha}a_{\beta}/a_{\beta}a_{\beta} \).

The expected frequency of each genotype in the \( F_2 \) progeny is as shown in Table 2.

Backcross matings of \( F_1 \) and parental S animals, ie, \( a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} \times a_{\alpha}a_{\alpha}/a_{\beta}a_{\beta} \), are expected to yield four genotypes with the frequencies shown in Table 2.

### F₂ Progeny

The working model predicts the frequencies of the \( F_2 \) phenotypes corresponding to the genotypes in Table 2: early onset of hypertension (genotype \( a_{\alpha}a_{\beta}/a_{\beta}a_{\beta} \), 0.1875; late onset of hypertension (genotype \( a_{\alpha}a_{\beta}/a_{\beta}a_{\beta} \), 0.5625; and normotension (\( a_{\beta}a_{\beta} \), 0.25. Furthermore, the ratio of the frequencies of early onset of hypertension in males and females is predicted to be 1.0. To test the predictions, eight matings of \( F_1 \) parents were performed in our facility. A total of 91 \( F_2 \) progeny were placed on the 8% NaCl diet at 28 days of age, and systolic blood pressures were estimated after 17 and 32 days. The results provide estimates of the frequency of early-onset hypertension (Table 3). Additionally, \( F_2 \) litters resulting from five of the matings were followed from 42 to 62 (average 50) days, a period long enough to estimate the frequency of late-onset hypertension in males but not in females. A comparison by \( \chi^2 \) analysis of the observed versus the predicted frequencies listed in Table 3 indicates that they are not significantly different (\( \chi^2 = 0.75, P > 0.50 \)). It is also noteworthy that the male-female frequency ratio for early-onset hypertension is 1.0, as predicted.

### TABLE 3. Predicted and Observed Phenotype Frequencies in \( F_2 \) and Backcross to S Progeny

<table>
<thead>
<tr>
<th>Group</th>
<th>Phenotype</th>
<th>Sex</th>
<th>Predicted, Phenotype/Total (Frequency)</th>
<th>Observed, Phenotype/Total (Frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ( F_2 ), observed</td>
<td>Early hypertension</td>
<td>Male</td>
<td>8.4/45 (0.1875)</td>
<td>7/45 (0.156)</td>
</tr>
<tr>
<td>32 days*</td>
<td></td>
<td>Female</td>
<td>8.6/46 (0.1875)</td>
<td>7/46 (0.152)</td>
</tr>
<tr>
<td>( F_2 ), observed</td>
<td>Late hypertension</td>
<td>Male</td>
<td>18/32 (0.5625)</td>
<td>16/32 (0.50)</td>
</tr>
<tr>
<td>42 to 62 days</td>
<td></td>
<td>Female</td>
<td>15/30 (0.50)</td>
<td>16/30 (0.53)</td>
</tr>
<tr>
<td>Backcross to S, observed</td>
<td>Early hypertension</td>
<td>Male</td>
<td>7.5/15 (0.50)</td>
<td>9/15 (0.60)</td>
</tr>
<tr>
<td>32 days</td>
<td></td>
<td>Female</td>
<td>(0.50)</td>
<td>(0.60)</td>
</tr>
</tbody>
</table>

S indicates salt-sensitive.

*Progeny of eight matings were followed for at least 32 days on the 8% NaCl diet. A subset of five of these \( F_2 \) litters containing 32 males was followed for 42 to 62 days (mean, 50 days), and the frequency of late-onset hypertension in males was determined. Female and backcross to S progeny were followed long enough to assess only early-onset hypertension.
Backcross to Parental S

The working model and genotypes listed in Table 2 also predict the frequencies of phenotypes in progeny of the backcross matings to parental S animals: early onset of hypertension, 0.5; late onset of hypertension, 0.5. Again, the frequency of early onset of hypertension in males is expected to equal that in females. Four matings of F1 and parental S rats in our facility yielded 45 progeny, which were studied as described in the preceding section, and the results are shown in Table 3. \( \chi^2 \) analysis indicates that the predicted and observed frequencies of the early onset of hypertension are not significantly different \((\chi^2=0.217, P>0.50)\), and the male-female frequency ratio is 0.88.

**Discussion**

The foregoing experimental evidence supports the model of inheritance of salt-dependent hypertension described in this report. The model is heuristic and predicts well the frequency of occurrence of three phenotypic responses to a high salt diet: early onset of systolic hypertension within 17 days, the parental S phenotype; late onset of systolic hypertension, which requires 50 to 60 days in males and more than 200 days in females; and maintenance of normal values, less than 140 mm Hg, the parental R phenotype. For the F2 male progeny of Table 3, for example, the predicted frequencies of early hypertensive, late hypertensive, and normotensive phenotypes are 0.1875, 0.5625, and 0.25, respectively, and the corresponding observed frequencies are 0.156, 0.50, and 0.34 (\( \chi^2=0.48, P>0.50 \)). While the results encourage use of the model as a framework for further studies, they do not exclude the possibility that additional genetic loci and more complex modes of inheritance may be involved. For example, Deng and Rapp reported cosegregation of blood pressure with angiotensin-converting enzyme and atrial natriuretic peptide receptor genes in F1 progeny of crosses of Dahl S and, respectively, Milan and Wistar-Kyoto strains; however, no polymorphisms of these genes between Dahl S and R strains were observed.

Several advantages are gained by defining the phenotypes according to the time required for the onset of hypertension rather than the level of blood pressure after a relatively long exposure to a high salt diet, eg, 24 weeks in the study of Knudsen et al. (In a subsequent study of the outbred Brookhaven strain fed an 8% NaCl diet, Dahl et al reported that of 10 males and 10 females, 0 and 2 animals survived to 24 weeks, respectively.) Confounding factors owing to secondary effects of the hypertension itself (ie, animal mortality and tissue damage, which can affect blood pressure values) are minimized. The number of animals that need to be maintained in the colony is decreased; therefore, the space and budget requirements are more affordable.

The time to onset of hypertension owing to a high salt diet may also provide insights into the pathophysiology. For example, Simchon et al reported that Dahl S rats develop salt-induced hypertension owing to two different hemodynamic mechanisms. After rats have been 4 weeks on an 8% NaCl diet, hypertension results from an increase in blood volume and cardiac output; total peripheral resistance is normal, although renal vascular resistance is increased. After 8 weeks of the diet, total peripheral resistance is increased and cardiac output is below normal. It is speculative but reasonable to hypothesize that the early and later hemodynamic patterns are determined by the genotypes (Table 2) underlying the early-onset and late-onset hypertensive responses, respectively. A testable consequence of this hypothesis is that F1 male progeny should exhibit only the later hemodynamic pattern of increased total peripheral resistance after 50 to 60 days on the high salt diet.

The identification and biochemical characterization of the genes corresponding to the \( \alpha \) and \( \beta \) loci are of evident importance. Although the genes are unknown, the possibility that the \( \beta \) locus is the renin gene or a gene closely linked to it is noteworthy. Rapp et al described a renin gene polymorphism in Dahl S compared with Dahl R rats that cosegregates with levels of systolic blood pressure in F2 progeny. Similar to the expression of the \( \beta \) locus described here, expression of the renin S gene allele in F2 males was noted after 8 weeks of the 8% NaCl diet and required a longer period of 11 weeks for comparable expression in the F2 females. How such renin gene alleles could account for the pathogenesis of salt-dependent hypertension remains unclear, however, since Dahl S rats have low renin levels in the plasma and kidneys.

Influences of sex on the arterial blood pressure levels of outbred Brookhaven and inbred Dahl strain rats are well documented. Our studies of the F1 progeny of reciprocal crosses (Figs 2 and 3) demonstrate that in the interval between 60 and 200 days on the 8% NaCl diet the blood pressure values of males significantly exceed those of females. The male-female difference, however, is diminished (S×R) or disappears (R×S) with a longer time on the diet. As noted above, Rapp et al observed that females of an F1 population of the inbred strains required a longer period on the 8% NaCl diet to express phenotypically the cosegregation of the S renin gene allele with levels of blood pressure similar to those of the males. We interpret our studies of the F1 progeny similarly to indicate that expression in the female of the dominant S allele at the \( \beta \) locus requires a longer exposure to the high salt diet or possibly further aging of the animal. The mechanism of the sex difference is unknown, but the observations of Dahl et al seem relevant. In studies of the outbred parental strains maintained on an 8% NaCl diet, the authors demonstrated that ovariectomy raised the blood pressure levels of the females to those of the males, while orchidectomy had no significant effect on the levels in males. Whether the ovaries influence the blood pressure levels directly by secretion of ovarian hormones or indirectly by modulation of growth hormone action, as suggested by Dahl et al, remains unknown. The mechanisms underlying the sex differences are amenable to further exploration, particularly in the F1 progeny described here.

The magnitude of the male-female difference in blood pressure was more than twice as great in F1 progeny of the S×R compared with the R×S cross (Figs 2 and 3). The values in Table 1 show that this is the consequence of higher pressure levels in males inheriting the \( \beta \) allele from the mother (S×R cross) compared with the father (R×S cross) and of higher pressure levels in females inheriting the \( \beta \) allele from the father (R×S cross) compared with the mother (S×R cross). Differential phenotypic expression of an allele depen-
dent on the sex of the donor parent is well recognized and generally ascribed to genomic imprinting.12,13 The possibility that the inheritance of salt-dependent hypertension involves genomic imprinting can be explored further by appropriate mating studies and by the molecular characterization of candidate genes for the \( \beta \) locus, eg, the renin gene.10,11 In the male animals, an alternative mode of inheritance must also be considered. A dominant \( \beta \) allele on the X chromosome could also explain the blood pressure differences in the F1 progeny. The model of inheritance described in this report provides a useful framework for further exploration of these possibilities.

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References

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