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Hypertension in the Spontaneously Hypertensive Rat Is Linked To the Y Chromosome

Daniel L. Ely and Monte E. Turner

The objective of our study was to determine the genetic influence on blood pressure in spontaneously hypertensive rats (SHR), and normotensive Wistar-Kyoto (WKY) rats using genetic crosses. Blood pressure was measured by tail sphygmomanometry from 8 to 20 weeks of age. Blood pressure was significantly higher from 12 to 20 weeks in the male offspring derived from WKY mothers \times SHR fathers as compared with male offspring derived from SHR mothers \times WKY fathers (180 ± 4 versus 160 ± 5 mm Hg, $p < 0.01$). There was no significant difference between the blood pressure of the F_1 females, further supporting Y chromosome linkage and not parental imprinting. The blood pressure data from F_2 males derived from reciprocal crosses of parental strains were consistent with the presence of a Y-linked locus, but not with an X-linked locus controlling blood pressure. The data strongly suggest that hypertension in the SHR has two primary components of equal magnitude, one consisting of a small number of autosomal loci with a second Y-linked component. (*Hypertension* 1990;16:277-281)

The spontaneously hypertensive rat (SHR) is a well-studied animal model of human essential hypertension. This inbred strain was developed by selective breeding of the Wistar-Kyoto (WKY) stock for higher blood pressure.¹ The response to this selection was rapid, with almost 100% hypertension by generation three.² This quick selective response indicates that only a few genetic loci were involved. This genetically selected SHR strain spontaneously and consistently develops moderate-to-severe hypertension between 7 and 15 weeks of age and has served as one model of genetic hypertension in humans.^{3,4} Several studies have shown that, although the SHR is stress responsive, it is actually quite resistant to elevated dietary sodium unless coupled with high stress.⁵⁻⁷ However, the genetic mechanism of hypertension in the SHR model is not yet understood, and comparative studies of various genetic hypertensive rat strains suggest several different pathogenic mechanisms.⁸ A few studies have used crosses of closely related strains and subsequent backcrosses that further support the idea that very few loci (from one to four) appear to be

involved in the development of SHR hypertension.⁹⁻¹² Also, a few studies have examined genetic markers of hypertension using different animal models.¹³⁻¹⁹ However, no consistent trends have emerged across rat models and specifically in the SHR as to the specific genes responsible for hypertension.

One of the more studied rat models with regard to the genetics of hypertension is the Dahl salt-sensitive (DS) and salt-resistant (DR) rat. In the DS rat there is no reported evidence for sex-linked loci controlling blood pressure.²⁰ Sex steroids do, however, exert effects as female DS rats show slower sodium-induced rises in blood pressure than males and castration of females altered their blood pressure to respond like that of males to salt.²¹ Endocrine studies have shown that the adrenals are necessary for the development of hypertension in DS rats,²² and genetic studies have shown that the characteristic steroid patterns of DS and DR rats are controlled by a single genetic locus (HYP-1) with two codominant alleles.¹⁴ However, there are other loci involved as the HYP-1 locus accounted for a 16 mm Hg blood pressure difference between DS and DR rats and the remaining difference was due to other unidentified genetic loci (see Reference 23 for a comprehensive review on DS and DR rats).

Also, in the psychosocial stress hypertension mouse model,²⁴ the rat model,^{2,25} and in human hypertension, there is higher blood pressure in males than females. The basic explanation for this sex difference has typically been a sex hormone differ-

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ence because after menopause the female incidence of heart disease and hypertension accelerates to match that of the male. However, research is lacking on the possible mechanism to explain this finding.

Therefore, the major objective of this study was to establish genetic crosses to elucidate potential genetic mechanism in the SHR that could explain the sex differences in blood pressures.

The breeding paradigm used in the present study is that suggested by Rapp²⁶ and has been successfully applied in determining relations between blood pressure and specific traits such as steroid profiles,¹⁴ vascular responsiveness,^{17,23,27} behavior patterns,²⁸ red blood cell membrane ion transport,^{29,30} sodium balance,³¹ and restriction fragment length polymorphisms for the renin gene in Dahl rats.³² Although we are not attempting at this time to correlate a specific trait with blood pressure, we will show evidence linking increased blood pressure with the Y chromosome, and therefore, the breeding paradigm used is important.

Methods

The parental strains were obtained from Harlan Sprague Dawley, Indianapolis, Ind., who obtained the initial breeding stock from the National Institutes of Health (NIH). According to the most current Harlan Sprague Dawley genetic monitoring report, these strains are comparable with most genetically authentic SHR and WKY rat strains found in the United States that were derived from the NIH colonies (personal communication, Harlan Sprague Dawley, November 1988). We have maintained the WKY rat stock in our lab for over 7 years, with approximately 21 generations of sib mating. G-banded karyotypes of SHR and WKY rat males were made using standard cytogenetic techniques.³³ Following standard genetic notation in all crosses and genotypes, the maternal partner (allele) is listed first.

Experiment 1

In experiment 1 the objective was to compare the systolic blood pressure of F₁ progeny of the two reciprocal SHR×WKY crosses with their respective parental strains (SHR or WKY rat). Reciprocal crosses were made between the two parental strains (SHR♀×WKY♂ and WKY♀×SHR♂) and the F₁ progeny were studied (males, *n*=26; females, *n*=20). A typical breeding box (40×50×20 cm) contained three females and one male of each combination housed in aspen shavings (American Excelsior, Cleveland, Ohio) and provided water and Purina lab chow ad libitum. Five breeding units for each hybrid cross were established (five nonsibling males and 15 females). Room temperature (26°–28° C), humidity (40–50%), and a 12-hour light/dark cycle were maintained. Bedding was changed once per week. Litters were weaned and sexed after 3 weeks and maintained by sibling group and sex for the duration of the experiments. The following groups of rats were used (*n*=8–12 per group): SHR, WKY rats, F₁ male and female hybrids from a WKY rat mother and SHR

father, and F₁ male and female hybrids from an SHR mother and WKY rat father. Blood pressures were measured weekly between 8 and 20 weeks of age by tail sphygmomanometry (Narco Biosystems physiograph and transducer, Houston, Tex.⁵). Each cage of rats was placed one at a time for 30 minutes in a warming chamber at 39° C and blood pressures were measured. This ensured minimum stress and general vasodilation. Weekly pressures and body weights were measured and tabulated by the same technician without knowledge of experimental objectives. To further verify the blood pressure differences observed after experiment 1, another replicate experiment using new F₁ males from both crosses (*n*=10/group) were studied identically as in experiment 1 but 1 year later. The intent was to verify the important results with different animals and at a different point in time (spring rather than fall).

Experiment 2

The primary objective of this experiment was to determine if the F₂ generation would maintain the same blood pressure differences as seen in the F₁ progeny and if the variability of pressures would increase in the F₂ progeny. The F₁ hybrid progeny within each reciprocal cross were bred and the F₂ generation was obtained. Blood pressure and body weight of these two F₂ male groups (*n*=8–12) were measured at weekly intervals (at 8–20 weeks of age) as described in experiment 1.

Statistical analysis was performed by analysis of variance and Student's *t* test to compare differences between groups. The animals were maintained under humane conditions according to the NIH guidelines.

Results

Figure 1 shows the average blood pressure of F₁ male hybrid offspring of the two reciprocal crosses, SHR parents and WKY rat parents. Male offspring with a hypertensive (SHR) father had significantly higher blood pressure than male offspring with a hypertensive mother (*p*<0.05 to *p*<0.001). The experiment was repeated 1 year later with different sets of parents (five males bred to 15 females). The same results were observed; F₁ males from a hypertensive father had significantly higher blood pressures (*p*<0.001) than F₁ males from a hypertensive mother (Figure 2).

In the F₂ generation, the origin of the Y chromosome and blood pressure were also consistent. The F₂ males with an SHR Y chromosome had blood pressures not significantly different from F₁ males with an SHR Y chromosome but significantly different (*p*<0.001) from either F₁ or F₂ males with a WKY rat Y chromosome (Figure 3). Because offspring should be affected regardless of sex, we measured blood pressure from week 8 to 20 in female offspring of the two reciprocal crosses. Karyotypes (G-banded) of SHR and WKY rat males were obtained and the Y chromosomes compared. No visible differences were

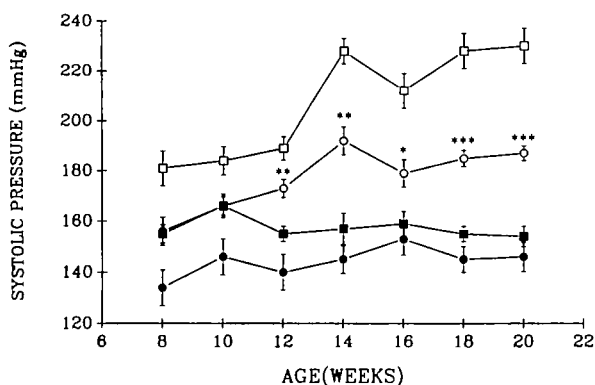


FIGURE 1. Line graph showing systolic blood pressure over time of the F₁ males derived from spontaneously hypertensive rat (SHR) ♀ x SHR ♂ (□), Wistar-Kyoto rat (WKY) ♀ x SHR ♂ (○), SHR ♀ x WKY ♂ (■), and WKY ♀ x WKY ♂ (●). Each group consisted of 8–10 rats, mean ± SEM. *p < 0.05, **p < 0.01, ***p < 0.001 compared with reciprocal cross-SHR x WKY.

observed. There was no significant difference between the blood pressures of F₁ females (Figure 4).

Discussion

Recently there is evidence that the WKY rats from different sources are not genetically identical.^{34–36} In this discussion we use WKY to designate our WKY rat strain that we have maintained in our lab with brother-sister matings for over 20 generations, and as such is homogeneous. The SHR and WKY rat strains are both highly inbred and should be essentially homozygous; as a result, the F₁ males from the two reciprocal crosses should be genetically identical for all autosomal loci. In general, they were heterozygous for all autosomal loci that differ between SHR and WKY rats. Thus, any autosomal loci influencing blood pressure would affect both groups of hybrid males similarly and could not account for the differences observed. The male offspring of the two crosses

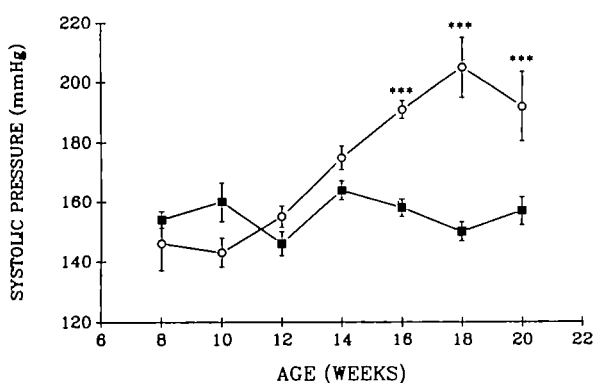


FIGURE 2. Line graph showing systolic blood pressure over time of F₁ male hybrids in a replication of the experiment in Figure 1 carried out 1 year later. F₁ males from a Wistar-Kyoto rat (WKY) ♀ x spontaneously hypertensive rat (SHR) ♂ (○) and F₁ males derived from a SHR ♀ x WKY ♂ (■). Each group consisted of 8–12 rats, mean ± SEM. ***p < 0.001 compared with each other.

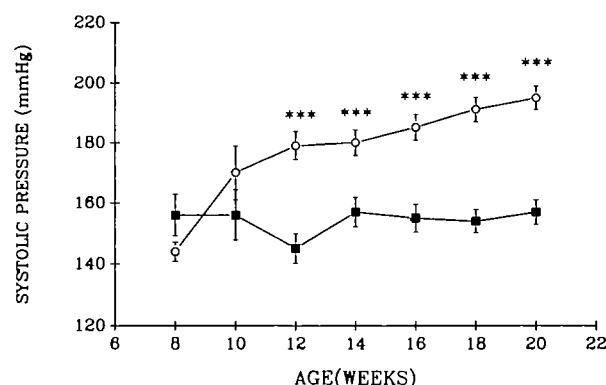


FIGURE 3. Line graph showing age-related systolic blood pressure in F₂ males derived from crossing the F₁ of Wistar-Kyoto rats (WKY) ♀ x spontaneously hypertensive rats (SHR) ♂ (○) or SHR ♀ x WKY ♂ (■). Each group consisted of 8–10 rats, mean ± SEM. ***p < 0.001 compared with each other.

differed only in the origin of their X and Y chromosomes (Table 1). If X chromosome loci were involved in blood pressure control in the SHR, the F₁ males should demonstrate blood pressure similar to that of their mother, and if Y chromosome loci were involved, the F₁ males should exhibit blood pressure similar to that of their father. Our data are only consistent with the latter hypothesis: F₁ male blood pressure was higher when the father was hypertensive than when the mother was hypertensive.

The F₂ males allow the testing of an alternative hypothesis on the influence of X chromosome loci. Although not intuitively appealing, it is possible that the WKY rat X chromosome contributes alleles that would increase blood pressure. In the WKY rat females, these are masked by other autosomal loci but are expressed in the F₁ males to increase blood pressure. In the F₂ in either cross, half of the males have an SHR X chromosome and half a WKY X chromosome (Table 1), such that any effect of the X chromosome would average out and only Y effects remain to account for the differences between the F₂

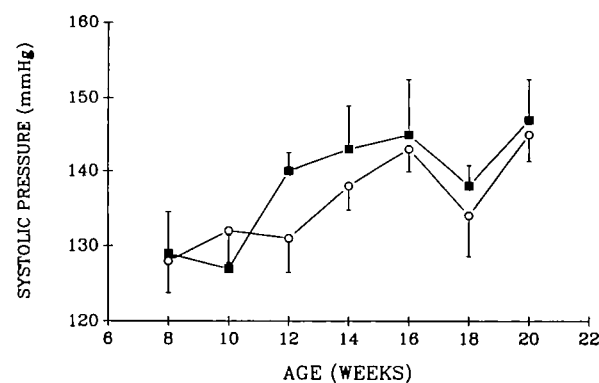


FIGURE 4. Line graph showing age-related systolic blood pressure in F₁ females derived from a Wistar-Kyoto rat (WKY) ♀ x spontaneously hypertensive rat (SHR) ♂ (○) and an SHR ♀ x WKY ♂ (■). Each group consisted of 10 rats, mean ± SEM (no significant differences).

TABLE 1. Origin of X and Y Chromosomes in Offspring of Two Reciprocal Crosses

Parents	SHR ♀ × WKY ♂ (XsXs × XwYw)	WKY ♀ × SHR ♂ (XwXw × XsYs)
F ₁		
Females	XsXw	XwXs
Males	XsYw	XwYs
F ₂		
Females	½XsXs ½XwXs	½XwXw ½XsXw
Males	½XsYw ½XwYw	½XsYs ½XwYs

SHR, spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; Xw and Yw, X and Y chromosomes of WKY rat origin (normotensive); Xs and Ys, X and Y chromosomes of SHR origin (hypertensive).

males in the two crosses; thus, the hypothesis that the WKY X chromosome contributes alleles that increase blood pressure is disproved.

A second possibility that could give results mimicking Y linkage without any true Y linkage is parental imprinting. In parental imprinting the phenotype of a gene (or translocation) differs depending on which parent, maternal or paternal, contributed the gene.^{37,38} Molecular data have indicated that in transgenic mice a differential methylation pattern occurs for an inserted *c-myc* oncogene. Only offspring who inherit the transgene from their father express the gene.³⁷

The potential exists that a hypertensive allele that is present in both males and females is only active when inherited from the male parent and this would mimic Y linkage. If the F₁ male blood pressures were the result of parental imprinting, females with a hypertensive father should have higher blood pressure than females with a hypertensive mother. There was no significant difference between the blood pressures of F₁ females (Figure 4), thus the effect is not consistent with parental imprinting. Our results definitely imply that a Y chromosome locus affects blood pressure in the SHR model.

The influence of the Y chromosome was unexpected, a priori, because the mammalian Y chromosome, other than the gene (or genes) required for male sex determination, contains few identified loci. The human Y chromosome has had only 14 loci mapped.^{39,40} Although the comparison is to the human Y because it is the genetically characterized Y chromosome, it is possible that the Y locus responsible in SHR hypertension is not on the human Y chromosome. Although the rat Y may differ somewhat in relation to the human Y chromosome, its basic structure should be similar. In retrospect, with the observations of variation within WKY rats^{34,36} and the quick response to selection (selection of males) in the origin of the SHR strain,² a Y locus is a simple solution. This only requires that the WKY rat stock used for selection was polymorphic for at least two Y chromosomes, one of which caused an

increased blood pressure. Variations for restriction fragment length polymorphisms have been identified in different inbred mouse strains⁴¹⁻⁴⁴ demonstrating that Y chromosomes in a species can differ.

The origin of this Y locus is not clear at this time. Two potential genetic mechanisms exist that can describe its origin, but we have no data to conclusively discard either. The first is that the SHR has a mutation in a locus normally found on the mammalian Y chromosome that either directly or indirectly increases blood pressure. We are currently investigating known loci on the mammalian Y chromosome for a relation with an autosomal blood pressure component. For instance, in the mouse the structural gene for male-enhanced antigen is on chromosome 17, and a Y-linked product enhances expression of this gene.⁴⁵ The second mechanism is a chromosome structural mutation, either the translocation of a locus raising blood pressure to the SHR Y chromosome or the deletion of a Y locus that modulates blood pressure in the WKY rat strain. If such a structural mutation did occur, it is small, because no visible differences were observed in G-banded Y chromosomes of the two strains.

The Y-linked component is not the only genetic component involved in SHR blood pressure regulation. An autosomal component must also be involved because both groups of F₁ hybrids had significantly higher blood pressure than the normotensive WKY rats. Further crosses are being done to elucidate the genetic mechanism of the autosomal component. Our data are consistent with the autosomal and Y-linked component acting in an additive manner with respect to each other. These data support earlier work suggesting that at least three major gene loci are involved in SHR hypertension^{9,11,13} and suggest at least two loci, one autosomal and one Y linked, are involved although additional autosomal loci are not inconsistent with our results.

In conclusion, the inheritance of SHR hypertension is composed of at least two genetic loci, one autosomal and one Y linked. The interaction of the two factors is additive. The implications suggest that this Y linkage can be important in isolating and identifying gene sequences that influence some forms of human essential hypertension.

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