Blood pressure and heart rate development in young spontaneously hypertensive rats

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Dickhout, Jeffrey G., and Robert M. K. W. Lee. Blood pressure and heart rate development in young spontaneously hypertensive rats. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H794–H800, 1998.—The course of hypertension development in young spontaneously hypertensive rats (SHR) was studied by the measurement of changes in systolic blood pressure (BP), body weight, and heart rate (HR) at 2, 3, 4, and 6 wk of age. To achieve this, we compared inbreeding lines of SHR and Wistar-Kyoto rats (WKY) to determine if differences in BP, body weight, or HR were present among inbreeding lines of the same strain or between strains. The effect of these differences on the eventual level of BP was then assessed. We found that BP began to diverge between SHR and WKY at 4 wk of age. Significant differences in systolic BP (24 mmHg) between SHR inbreeding lines at 4 wk of age did not affect the BP at 8 wk (172 vs. 170 mmHg). Pulse pressure was significantly higher in SHR than in WKY at 4 wk of age. HR was elevated in SHR over age-matched WKY at 3 wk of age and positively correlated to the level of BP attained by individual animals at 6 wk (P = 0.037). Moreover, WKY inbreeding lines showing elevated HR developed higher BP (145 vs. 127 mmHg) at 10–12 and 20 wk of age. The prehypertensive tachycardia in SHR was investigated further and found to result from an increased intrinsic HR. Because HR at 3 wk is a genetic trait that can be partitioned into inbreeding lines, and inbreeding lines most expressive of this trait showed the highest eventual BP, we conclude that prehypertensive tachycardia may be an important first step during hypertension development in SHR. Moreover, early elevations in HR are highly predictive (r = 0.41) of hypertension occurrence in the animal population studied.

Wistar-Kyoto rats; prehypertensive tachycardia; pulse pressure; inbreeding

ESSENTIAL HYPERTENSION results from the culmination of a series of pathological changes in the body that lead to a sustained elevation of blood pressure (BP). The spontaneously hypertensive rat (SHR) is a suitable model to study hypertension development because it is similar to humans with essential hypertension. These similarities include a genetic predisposition to high BP without specific etiology, increased total peripheral resistance without volume expansion, and similar responses to drug treatment (12).

A precise knowledge of early BP development is essential to understand hypertension as a disease process. For a causal role to be ascribed to a defect, this defect should occur at the initiation of BP elevation. Defects that occur only after large BP elevations should be considered secondary to the disease process (17). Previous studies of young SHR BP development have yielded conflicting results. Some observers found that SHR and Wistar-Kyoto rats (WKY) had similar BP at or before 4 wk of age (19, 28, 32), whereas others found a significant difference in BP at 3 wk of age (18) or at birth (13, 14). The reason for these contradictory findings is unclear. However, in most of these studies, the sample size was small (n ≤ 10), and distinctions between inbreeding lines within the strains were not made.

With inbred animals such as SHR and WKY, the genetic variation of the population typically found continuously between individuals becomes partitioned between inbreeding lines (8). Between-line differences within a strain can occur by chance and may be unrelated to the genetic differences responsible for hypertension in SHR. However, these genetic differences may result in significantly different BPs between given inbreeding lines of animals. Therefore, BP differences found between young SHR and WKY in some studies may be due to the effect of random genetic drift within the strains acting on the specific inbreeding lines tested. The question then is whether the early, small but statistically significant difference in BP between the tested lines of SHR and WKY would affect the eventual outcome of hypertension. Furthermore, it is not known whether the differences among the inbreeding lines tested would hold for the population as a whole if a greater number of lines were tested. These questions were examined in this study.

Changes in heart rate (HR) during SHR development may also be important in the pathogenesis of hypertension. Prehypertensive tachycardia has been reported in SHR (28, 33). An increased HR would suggest an early elevation in cardiac output if stroke volume remained constant or increased with HR. A previous study found that stroke volume was maintained constant with increasing HR in 6-wk-old SHR. Cardiac output increased linearly with HR from 350 beats/min at rest to 460 beats/min under stress (24). SHR have also shown an increased cardiac index at an early age, which later returned to normal, leaving an increased mean arterial pressure and total peripheral resistance (30).

Body weight change is another aspect of SHR development that has received little attention. Differences in body weight have been found between young SHR and WKY. Young SHR were lighter than age-matched WKY (3, 31). The reason for this is unclear, but this trait cosegregated with hypertension in the F2 progeny of crossbred SHR and WKY (26). Such a difference could be a sign of some underlying metabolic irregularity in SHR, leading to hypertension.

The main purpose of this study was to describe in detail the course of physiological development in SHR compared with its normotensive control WKY, with an emphasis on how this development relates to the pathogenesis of hypertension. This was accomplished.
by measuring the developmental changes in systolic BP, HR, and body weight between inbreeding lines of SHR and WKY and then comparing these parameters with the severity of hypertension in the adult. Differences in developmental parameters between inbreeding lines that resulted in differences in disease outcome were considered significant in hypertension development. The underlying cause of the prehypertensive tachycardia found in SHR was also explored by analyzing the baroreflex, the level of autonomic drive influencing HR, and the measurement of plasma levels of epinephrine and norepinephrine.

METHODS

Developmental study. Male SHR and WKY at 2, 3, 4, and 6 wk of age were used for BP, HR, and body weight measurements. The number of inbreeding lines and total number of individuals for the respective strains are indicated in Table 1. The animals were obtained from colonies maintained at McMaster University's Animal Quarter. These colonies were originally derived from the Charles River strains, and we have maintained them in our institute by continuous full-sibling inbreeding for >10 yr (>20 generations). The rats were weaned at 3 wk of age and were housed with their littermates, two to four animals per cage, and food and water were available ad libitum. The care of these animals was in accordance with the guidelines of the Canadian Council on Animal Care.

Rats were weighed, and their systolic BP was measured using the indirect method of tail-cuff occlusion in conscious animals. HRs were calculated from the physiological tracings obtained during BP measurements. Origins of the rats were noted as individual, inbreeding line, and strain so that results could be analyzed to see if strain or line effects were significant for the parameters measured.

Some inbreeding lines showing aberrant developmental characteristics for their strain at 4 wk of age were followed into adulthood to see if these differences affected BP. SHR lines that showed significant differences in systolic BP at 4 wk of age were maintained until hypertension developed to find the effect of early BP differences on disease outcome. Similarly, WKY lines that showed significant elevation in HR were maintained to find the effect of BP outcome.

Acute study in 4-wk-old rats. In addition to the indirect measurement of systolic BP and HR, direct measurements of systolic, diastolic, and mean arterial BP and HR were made at 4 wk of age as follows. The ages of SHR and WKY used for these experiments varied from 27 to 31 days and were chosen in a way that resulted in equal means between the groups. Initial experiments were carried out to standardize the anesthesia protocol to avoid cardiovascular depressive effects of anesthesia. These experiments consisted of comparing results of systolic BP measurements using the indirect method in conscious rats with measurements using the direct method in rats under anesthesia. A combined anesthesia consisting of ketamine as a preanesthetic and urethane as an inducer was used. Ketamine was chosen as a preanesthetic because it produces deep sedation and thus reduces the dose of the general anesthetic required (11). Urethane was chosen as an inducer because previous studies have shown that it has little cardiovascular-depressive effect at low doses (6, 25). The dosages that did not affect the systolic BP of the rats were found to be 75 mg/kg ketamine ip with 0.25 g/kg urethane sc for WKY (n = 9) and 50 mg/kg ketamine ip with 0.50 g/kg urethane sc for SHR (n = 10). SHR and WKY were therefore anesthetized using these different doses for femoral artery cannulation to measure HR and systolic, diastolic, and mean arterial BP directly. The results were recorded on a Digi-Med BP analyzer (Micro-Med, Louisville, KY) attached to a microcomputer for continuous digital data storage, allowing the sampling of mean BP and HR at 3 kHz. The values were averaged over 5-s intervals to record the incremental changes.

Investigation of tachycardia. Prehypertensive tachycardia found in SHR was investigated pharmacologically to detect if it was due to excessive sympathetic excitation, a lack of parasympathetic tone, an exaggerated baroreflex, or other hormonal factors influencing the intrinsic HR. SHR and WKY were anesthetized with ketamine-urethane. The left femoral artery was cannulated and recordings were made on the Digi-Med BP analyzer. HR was determined during sympathetic blockade with the cardiac selective β1-receptor antagonist atenolol (0.5 mg/kg), parasympathetic blockade with the muscarinic receptor antagonist atropine sulfate (0.4 mg/kg), and complete autonomic blockade by combining atenolol (0.5 mg/kg) and atropine sulfate (0.4 mg/kg). The baroreflex response was measured by recording HR responses to sudden changes in BP, stimulated by intravenous infusion in a stepwise manner of increasing doses of sodium nitroprusside (6.2, 12.5, and 25 µg/kg) or phenylephrine hydrochloride (1.5, 3.1, 6.2, 12.5, and 25 µg/kg). The values of BP reached and changes in HR produced were averaged for each of the given doses in each of the strains.

To investigate further the sympathetic influence on HR, we collected blood samples from 4-wk-old rats for the measurement of catecholamine content. Samples were collected in sodium citrate and centrifuged to obtain plasma for analysis by high-performance liquid chromatography (HPLC). 3,4-Dihydroxybenzylamine was added as a biogenic amine internal standard. EDTA was added as an antioxidant and aluminacetic acid extraction was performed on samples before loading on an HPLC column (20). The HPLC was equipped with an electrochemical detector, and peak integration was performed semiautomatically on a microcomputer.

Table 1. Developmental parameters for SHR and WKY at 2, 3, 4, and 6 wk of age

<table>
<thead>
<tr>
<th></th>
<th>2 wk</th>
<th>3 wk</th>
<th>4 wk</th>
<th>6 wk</th>
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<tbody>
<tr>
<td>Body wt, g</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>SHR</td>
<td>22±1 (5, 15)</td>
<td>39±2 (10, 25)</td>
<td>63±2 (20, 40)</td>
<td>133±4 (7, 20)</td>
</tr>
<tr>
<td>WKY</td>
<td>26±1 (5, 15)</td>
<td>44±1 (10, 25)</td>
<td>63±2 (20, 40)</td>
<td>120±5 (7, 20)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>93±6 (5, 15)</td>
<td>110±5 (10, 25)</td>
<td>127±3* (20, 40)</td>
<td>148±3* (7, 20)</td>
</tr>
<tr>
<td>WKY</td>
<td>96±5 (5, 15)</td>
<td>103±3 (10, 25)</td>
<td>118±3 (20, 40)</td>
<td>120±5 (7, 20)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>397±8* (5, 15)</td>
<td>430±7* (10, 25)</td>
<td>441±4* (20, 40)</td>
<td>398±5 (7, 20)</td>
</tr>
<tr>
<td>WKY</td>
<td>373±9 (5, 15)</td>
<td>380±5 (10, 25)</td>
<td>407±5 (20, 40)</td>
<td>392±7 (7, 20)</td>
</tr>
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</table>

Values are means ± SE; no. of inbreeding lines and total no. of individuals are given in parentheses for respective strains (inbreeding lines, individuals). BP, blood pressure; SHR, spontaneously hypertensive rats. *Significantly different from age-matched Wistar-Kyoto rats (WKY) (P < 0.05).
Statistical analysis. Values given are means ± SE. Data analysis was performed with the computer-based statistical package SAS (SAS Institute). Mixed-model analysis of variance, with fixed effects as strain type (SHR vs. WKY) and random effects as inbreeding lines nested inside strain type, was used to test the hypotheses of unequal means for the developmental parameters measured at 2, 3, 4, and 6 wk of age for strains or inbreeding lines. Line effects were treated as random effects because the division of additive genetic variance into inbreeding lines could produce an infinite number of such inbreeding lines, and thus the inbreeding lines actually tested were only a sample of the population of such lines. Animals within inbreeding lines were treated as independent observations regardless of litter of origin, so differences among these animals comprise the random error when line differences were tested in the F statistic. Means were compared with Fisher’s protected least significant differences (LSD) through multiple comparison tests.

An analysis of covariance (ANCOVA) was performed in SHR and WKY with systolic BP at 6 or 10 wk as the dependent measure, inbreeding line as the independent measure, and HR at 3 or 4 wk as the covariant to test the hypothesis that differences existed between inbreeding line mean systolic BP and that HR was a predictor of this phenomenon. Means were compared with Fisher’s protected LSD multiple comparison test.

All other comparisons were performed by unpaired t-test for significant differences between the strains. Significance was recognized at P < 0.05.

RESULTS

Developmental study. Body weight of SHR was less than WKY at 2 and 3 wk of age. At 4 wk, body weight was similar between SHR and WKY, and at 6 wk SHR had become heavier than WKY (Table 1). However, differences between inbreeding lines within the strains contained most of the variation in this parameter over all age groups (Table 2). This indicates that there was a greater difference within the strains for body weight than between strains. None of the body weight differences between the strains reached statistical significance when between-line differences were taken into account (Table 2).

Indirect BP measurements. Systolic BP was similar between SHR and WKY at 2 and 3 wk of age. Differences were small at 4 wk but were statistically significant (P = 0.02), and by 6 wk systolic BP in SHR had become significantly elevated compared with that in WKY (P = 0.005) (Table 1). At 2 wk, most of the variation in systolic BP was found between individuals. At 3 and 4 wk, differences between inbreeding lines accounted for most of the variation in systolic BP, with differences between strains smaller than those between lines. However, by 6 wk, differences between strains overshadowed the differences between inbreeding lines (Table 2).

HR was significantly higher in SHR compared with that in WKY at 2 wk (P = 0.02), 3 wk (P = 0.0001), and 4 wk of age (P = 0.0001), but this difference was absent by the 6th wk (Table 1). At 2 wk most of the variation in HR was between individuals. At 3 wk, strain differences dominated, and by 4 wk, differences between the strains and inbreeding lines were both significant. By 6 wk of age, individual differences again accounted for most of the variation in HR (Table 2).

A small increase in HR was noted in the WKY at 4 wk over the 3 wk level (Table 1). Fisher’s protected LSD test showed that the WKY population consisted of two groups that accounted for the significant differences found between inbreeding lines. One group consisting of three lines showed HR approaching the SHR level and produced the slight elevation in HR seen in the WKY strain at 4 wk. The other group consisted of seven lines and showed no elevation in HR over the 3 wk level.

The overall pattern of systolic BP and HR development is shown in Fig. 1. The period of prehypertensive tachycardia for SHR was found between 2 and 4 wk. The subsidence of tachycardia and an increase in systolic BP of SHR compared with that in WKY became apparent in rats older than 4 wk.

Direct BP measurements. Direct measurements of hemodynamic parameters were carried out in 4-wk-old rats. In this instance, systolic BP was not significantly different between the strains with the mean value of 127 ± 6 mmHg in SHR (n = 5) vs. 117 ± 6 mmHg for WKY (n = 9). Similarly diastolic BP was not significantly different with the mean value of 84 ± 14 mmHg in SHR (n = 5) vs. 86 ± 12 mmHg for WKY (n = 7). However, pulse pressure was significantly greater in SHR (43 ± 4 mmHg, n = 5) than in WKY (28 ± 3 mmHg, n = 7, P = 0.02). HR was also significantly higher in SHR (43 ± 31 beats/min, n = 5) than in WKY (389 ± 17 beats/min, n = 7, P = 0.03).

Effect of between-line differences on outcome of hypertension. At 4 wk of age statistically significant differences existed for inbreeding lines from SHR for systolic BP and from WKY for HR (Table 2). These line differences were isolated by Fisher’s LSD test, allowing the testing of these line differences on hypertension outcome. SHR from inbreeding lines 7 and 12 differed significantly in systolic BP (P = 0.006). Line 7 showed lower-than-average systolic BP (103 ± 1 mmHg, n = 3).

Table 2. Analysis of developmental parameters for SHR and WKY at 2, 3, 4, and 6 wk of age

<table>
<thead>
<tr>
<th>Comparison Groups</th>
<th>Parameter Variation, %</th>
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<tbody>
<tr>
<td></td>
<td>2 wk</td>
</tr>
<tr>
<td>Body wt</td>
<td></td>
</tr>
<tr>
<td>Strain</td>
<td>21</td>
</tr>
<tr>
<td>Line</td>
<td>41*</td>
</tr>
<tr>
<td>Individual</td>
<td>38</td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
</tr>
<tr>
<td>Strain</td>
<td>0.4</td>
</tr>
<tr>
<td>Line</td>
<td>22</td>
</tr>
<tr>
<td>Individual</td>
<td>78</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
</tr>
<tr>
<td>Strain</td>
<td>11*</td>
</tr>
<tr>
<td>Line</td>
<td>10</td>
</tr>
<tr>
<td>Individual</td>
<td>79</td>
</tr>
</tbody>
</table>

Values are percentage of variation in measured parameter found between different rat groups: strain, variation in SHR vs. WKY; line, variation among inbreeding lines of SHR and WKY; individual, individual variation within inbreeding lines. No. of inbreeding lines and total no. of individuals are same as those in Table 1 at each of the age groups. *Significantly different (P < 0.05).
Investigation of prehypertensive tachycardia. Baroreflex bradycardia caused by phenylephrine-induced BP increase was similar between the two strains (Fig. 2). However, baroreflex tachycardia caused by sodium nitroprusside-induced BP decrease was significantly less in SHR than in WKY (Fig. 2). Complete autonomic blockade by atropine sulfate and atenolol resulted in a significantly higher mean intrinsic HR in SHR (411 beats/min) than in WKY (365 beats/min, Fig. 3). We used the difference between the basal HR (Table 1) and the intrinsic HR (Fig. 3) as the net autonomic tone in these animals. The sympathetic tone as tested by atenolol infusion was higher in the SHR than WKY when expressed as either an absolute number (SHR = 95 and WKY = 74 beats/min) or as a percentage of intrinsic rate (SHR = 23% and WKY = 20%). However, this difference did not reach the level of statistical significance. The sympathetic component of the autonomic tone in both strains at this age increased the intrinsic HR an average of 16 beats/min in WKY and 31 beats/min in SHR. After removal of all autonomic tone, SHR still showed a significantly higher intrinsic HR than that in WKY (Fig. 3). The parasympathetic component of the autonomic tone was tested by atropine sulfate infusion so the increase in HR over the basal rate showed the magnitude of the parasympathetic tone, which is expressed as a negative value. The parasympathetic tone expressed as either an absolute number (SHR = −64 beats/min and WKY = −62 beats/min) or as a percentage of the intrinsic rate (SHR = −16% and WKY = −17%) showed little difference between the strains.

Analysis of plasma catecholamines from 4-wk-old rats showed the levels of epinephrine (0.73 ± 0.3 ng/ml in SHR and 1.4 ± 0.3 ng/ml in WKY, n = 7) and norepinephrine (1.9 ± 0.2 ng/ml in SHR and 1.6 ± 0.2 ng/ml in WKY, n = 7) did not significantly differ between the strains.

**DISCUSSION**

The major findings of this study are as follows. A significantly higher HR was present in SHR compared vs. the average systolic BP found for the entire population represented by line 12 (127 ± 4 mmHg, n = 4). Data collected from the same animals at 8 wk of age revealed no difference in BP although both lines displayed BP that were clearly hypertensive. Average systolic BP in line 7 was 172 ± 4 mmHg (n = 3), and BP in line 12 was 170 ± 6 mmHg (n = 4).

WKY lines 1, 3, and 7 showed a significant elevation of HR (combined mean 429 ± 10 beats/min, n = 10, P = 0.001) over the combined mean for the remainder of the WKY lines (394 ± 5 beats/min, n = 24). These tachycardic lines also showed significant BP elevations at 10 wk (145 ± 7 mmHg) compared with age-matched WKY rats with no history of HR elevation (127 ± 2 mmHg, P = 0.01). This elevated BP remained at 20 wk of age (144 ± 5 mmHg, P = 0.005).

ANCOVA was performed within the SHR and WKY strains with systolic BP as a dependent measure, inbreeding line as the independent measure, and HR as a covariant to assess the value of early elevated HR as a predictor of elevated BP. When HR at 3 wk was used as a covariant for systolic BP at 6 wk in SHR, no significant differences between the systolic BP for inbreeding lines of SHR were found. However, when HR at 4 wk was used as a covariant for systolic BP in WKY at 10 wk, significant line differences were found. The regression analysis showed that line differences alone accounted for 38% of the variation in systolic BP. The addition of the covariant (4-wk HR) increased the variation accounted for in the dependent to 79%. Therefore, the covariant HR accounted for 41% of the variation in systolic BP.

To test in a mixed population of hypertensives and normotensives if HR elevation at 3 wk is a predictor of hypertension, we performed correlation analysis between HR at 3 wk and systolic BP at 6 wk, combining the individuals of both strains. A positive correlation was found (P = 0.037, n = 26). The correlation was linear with even distribution of residuals around the predicted line (r = 0.41).

**Fig. 1. Systolic blood pressure and heart rate profiles of spontaneously hypertensive rats (SHR; •) and Wistar-Kyoto rats (WKY; ○) during early development. No. of inbreeding lines and total no. of individuals for SHR and WKY at different age groups are listed in Table 1. BPM, beats/min.**
with WKY before any difference in BP could be detected. BP began to diverge between the strains at 4 wk of age. A small but statistically significant difference in BP between inbreeding lines of SHR (24 mmHg at 4 wk of age) had no effect on the eventual outcome of hypertension (both groups attaining \(170\) mmHg by 8 wk). However, WKY inbreeding lines that exhibited a significant elevation in HR at 4 wk developed a significantly higher BP than those without previous HR elevation. HR at 4 wk when used as a covariant accounted for 41% of the variation in systolic BP of WKY at 10 wk. An overall positive correlation between HR at 3 wk of age and the level of BP at 6 wk was also found, indicating the predictive value of elevated HR for BP development in the animal population studied.

Earlier studies that described a significant difference in BP between WKY and SHR at 3 wk of age (18) or at birth (13, 14) were based on the measurement of a few animals. Lais et al. (18) studied six littermates consisting of both males and females at 3 wk of age. The animals from the SHR strain had undergone 22–26 generations of full-sibling inbreeding (18). At this level of inbreeding, the probability that any genetic locus was fixed was >95% (9). The genetic variance usually found continuously between individuals becomes partitioned among inbreeding lines, and the genetic variance of the whole population had approximately doubled, according to the following calculation:

\[
\text{Genetic variance between inbreeding lines} = 2 \times F \times V_g = 1.972V_g
\]

\[
\text{Genetic variance between individuals} = (1 - F) \times V_g = 0.014V_g
\]

\[
\text{Total population genetic variance} = (1 + F) \times V_g = 1.986V_g
\]

where \(F\) is the coefficient of inbreeding and \(V_g\) represents the variance in the base population before inbreeding. \(F = 0.986\) after 20 generations of full-sibling inbreeding (10).

In this situation, genetic differences between inbreeding lines within the same strain are exacerbated. However, whether these differences affect the eventual outcome of hypertension is unknown. To test for between-strains differences in developmental parameters such as BP, several lines of the same strain must be sampled to estimate the variance within the whole population. A conservative estimate of the number of degrees of freedom in a model would be the number of inbreeding lines tested, not the number of individuals (5). Because this was not done by Lais et al. (18) for 3-wk-old rats, the differences found may simply represent significant differences between the inbreeding lines tested, not differences between the hypertensive and normotensive populations as a whole. Furthermore, in this study, we found that the major component of variation in systolic BP was between inbreeding lines at this age and not between the SHR and WKY strains. Difference in BP put forth by Gray (13, 14) at birth falls into a similar category because the number of inbreeding lines in each strain tested was not stated.

The parameters we have measured (BP, HR, body weight, and pulse pressure) are not merely the product of genetic variance between strains, lines, and individuals. These parameters are also affected by environmental variance occurring in the colony and contain some random error components due to inaccuracies of measurement. Because the majority of genetic loci in the tested lines should have been fixed after more than 20 generations of full-sibling inbreeding (9), the parameters measured with high individual variance represent characteristics not strongly genetically determined. At 3 and 4 wk of age the percentage of individual variation is lowest for HR, followed by body weight and systolic BP.

Systolic BP is the least genetically determinate parameter at 2, 3, and 4 wk of age. However, by 6 wk, it becomes the parameter that is most genetically determined (Table 2). The fact that significant differences in systolic BP between SHR inbreeding lines (25 mmHg at 4 wk) had no effect on the eventual severity of hypertension in these animals confirms the lack of genetic determinance of this characteristic at an early age and suggests that the hypertension disease process occurring in SHR has not yet become fully manifest. This assertion is supported by the finding of structural changes in SHR resistance vessels at this age, which may lead to an increased total peripheral
resistance but is accompanied by a delayed functional maturity of the arteries (7).

Body weight was moderately dependent on changes in environmental factors occurring in the colony at different times. This dependence decreased with age. SHR body weight was less than that of WKY at 2 and 3 wk of age, became similar at 4 wk, and exceeded WKY body weight at 6 wk. Therefore the rate of body growth was significantly greater in SHR than in WKY over this period. This may represent an important trend in the development of hypertension in SHR. The age of maximum weight gain in SHR and WKY has been shown to coincide with the period of maximum BP rise in these rats (29). This seems to indicate that the surge in BP per body weight gain in SHR and WKY has been shown to coincide with the period of maximum BP rise in these rats (29). Therefore the greater rate of weight gain in SHR may be responsible for the greater surge seen in systolic BP in SHR compared with that in WKY.

The most genetically determined parameter in the SHR and WKY at 3 and 4 wk of age was HR. This aspect was reflected by the differences between the strains, with SHR having elevated HR, and among the different lines within WKY. Once hypertension had become established in SHR, HR had returned to WKY levels. Significant HR differences among WKY inbreeding lines were also significantly related to systolic BP outcome. Inbreeding lines of WKY with higher HR displayed significantly elevated systolic BP at 10 and 20 wk of age. Because elevated HR in SHR occurred before BP elevation, elevated HR may be considered a primary process in the development of hypertension in SHR by the criteria put forth by Korner and Swales (16). This points to other factors such as thyroxine, which may be responsible for the prehypertensive tachycardia found in SHR.

The mechanism behind elevated HR affecting hypertension development is unknown. The increased HR and/or increased pulse pressure that we found in 4-wk-old SHR may act as a direct mechanical stimulus to vascular growth, which could result in the increased volume of medial smooth muscle found in the resistance blood vessels of young SHR (7). In the pial arteries from Sprague-Dawley rats, vascular hypertrophy was produced by an elevation of pulse pressure alone when mean arterial BP was not significantly different between sham and clipped rats (2). Other studies have also found that in SHR a reduction in the pulse pressure and HR during antihypertensive therapy may be important in preventing the development of abnormal small artery structure in hypertension (4).

Increased HR may also lead to increased cardiac output as it did in stressed SHR (24). An increased cardiac index in the early stages of hypertension development (i.e., 34 to 41 days of age) has been noted in SHR (30), and SHR displayed a rightward shift in pressure-flow curves compared with WKY at 6 and 9 wk of age. This suggests that some structurally based long-term autoregulatory mechanism was present in the vasculature of SHR to normalize flow with increased pressure (1). In the whole animal, however, reducing HR with the nonselective β-blocker nadolol by dosing from birth to 28 wk did not prevent hypertension, nor did it reduce cardiac or resistance vessel hypertrophy (23). Therefore, it seems unlikely that tachycardia alone could bring about hypertension because the correction of this abnormality did not correct the hypertension. Therefore, this defect did not satisfy all the postulates for causality put forth by Korner and Swales (17). Other factors, such as changes in the vascular growth factors or metabolic changes, may be involved.

The surge in HR found in young SHR could represent a surge in sympathetic output because our previous study using sympathectomy and adrenalectomy was found to abolish hypertension in the SHR (21). However, the use of pharmacological blockade in our current study indicates that prehypertensive tachycardia in the SHR is mostly due to an increase in intrinsic HR. Furthermore, plasma levels of norepinephrine and epinephrine were not elevated in these rats at 4 wk. This points to other factors such as thyroxine, which may be responsible for the prehypertensive tachycardia found in SHR.

Our finding that tachycardia in prehypertensive rats is a good predictor of eventual BP outcome is quite similar to the situation in humans. In humans, several studies have shown that faster resting HRs are associated with higher BP levels and that this association is observed across the whole range of BPs in the general population and is present at any age (27). An increased HR is typical for young patients with borderline hypertension, and a faster HR has also been found in the offspring of hypertensive families, suggesting that the increase in HR in hypertension is a marker of an underlying disorder that affects BP and HR in a parallel fashion (27). More importantly, several epidemiological studies have confirmed the predictive role of HR in the development of hypertension (27). The mechanism associated with the increase in HR in humans is not known. An overactive sympathetic activity in some of these patients (~25% of subjects with borderline hypertension), on the basis of presence of elevated norepinephrine levels, may be one of the contributing factors (27). Our results on prehypertensive SHR suggest that intrinsic HR increase is a major cause of tachycardia in these animals.

In this study, we found that young SHR at 4 wk of age showed a depressed baroreflex response to BP reduction. This is similar to previous studies on young adult SHR (8 wk old) (16). However, these results differed from those in 6-wk-old SHR, in which SHR were found...
to exhibit an increased baroreflex slope in the mean arterial BP-HR plot compared with WKY, but the maximum and minimum HRs were similar between the strains (15). The reduced gain in HR we have observed in the 4-wk-old SHR in response to pressure drop may be a result of the preexisting elevated HR. This may limit the amount of sympathetic drive that can further increase HR because increasing HR beyond certain levels would result in a decrease in stroke volume and negatively impact on cardiac output.

In conclusion, we have found that HR elevation precedes BP elevation in SHR, and prehypertensive tachycardia may be an important first step during hypertension development in SHR.

We thank Dr. S.L. Kyone for technical assistance.

This study was supported by a grant-in-aid from the Heart and Stroke Foundation of Ontario. Dr. Kyone was the recipient of a Heart and Stroke Foundation/Medical Research Council Farquharson Scholarship Award as a medical student in 1994.


Received 13 June 1997; accepted in final form 13 November 1997.

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