Cardiac Mass and Peripheral Vascular Structure in Hydralazine-Treated Spontaneously Hypertensive Rats

Lennard T. Jespersen, Niels C. B. Nyborg, Ole Lederballe Pedersen, Erich O. Mikkelsen, and Michael J. Mulvany

Summary We have examined the effect of antihypertensive treatment on heart weight and on structural and functional characteristics of isolated mesenteric resistance vessels (internal diameter 170–220 μm) in spontaneously hypertensive rats (SHR) and in Wistar-Kyoto rats (WKY). The SHR and WKY were treated with hydralazine from the age of 4 weeks and were examined at ages 12 to 14 weeks and 23 to 27 weeks. Treated SHR had a mean blood pressure as much as 29% below that of control WKY, which in turn was 25 to 40% less than that of control SHR. In 12- to 14-week-old rats the heart to body weight ratio (which in control SHR was 13% greater than that of WKY) was unaffected by treatment. Thereafter, the heart to body weight ratio of treated SHR did not increase as much as usual. At both ages, the media thickness and contractile response of the resistance vessels of the SHR (which were, respectively, 37% and 30% greater than those of vessels of WKY) were unaffected by treatment. However, because treatment caused a small (8%) increase in the lumen diameter of the vessels of the SHR, treatment did cause small, but possibly physiologically important, decreases both in the media to lumen ratio (11%) and in the pressure against which these vessels would have been able to contract (10%). Treatment had little effect on the pharmacological characteristics of vessels of either SHR or WKY. The results suggest that the increased heart weight, media thickness, and contractile response in mesenteric resistance vessels of SHR up to ages 23 to 27 weeks are due primarily to factors other than increased pressure. (Hypertension 7: 734-741, 1985)

Key Words • cardiovascular structure • calcium, norepinephrine • resistance vessel • smooth muscle

It is well established that the hypertensive state is associated with structural abnormalities in the cardiovascular system. These abnormalities include cardiac enlargement, increased wall to lumen ratio in arteries and resistance vessels, increased relaxed peripheral resistance, and decreased venous compliance. Furthermore, these changes are seen at an early stage of hypertension, which suggests that they may play a role in the pathogenesis of the disease and are not just an adaptive change to the increased pressure.

One way of assessing the possible contribution of cardiovascular abnormalities to the development of hypertension is to determine the effect of antihypertensive therapy on the abnormalities. The present study was initiated to investigate this question in a model of human essential hypertension, spontaneously hypertensive rats (SHR). The aim was to determine whether preventing the development of high blood pressure in SHR, by antihypertensive treatment from an early age, would inhibit the development of the structural abnormalities that we have previously observed in these animals: increased heart to body weight ratio, increased resistance vessel media to lumen ratio, and increased resistance vessel contractility. Hydralazine was chosen as the antihypertensive drug since it has previously been shown to reduce blood pressure, primarily through its effect to decrease the peripheral resistance. The animals were treated from the age of 4 weeks, at which age there is only a small elevation of blood pressure, and the parameters were measured in young adult animals aged 12 to 14 weeks, when the hypertension normally has fully developed, and then again in mature animals aged 23 to 27 weeks, to determine if long-term treatment could maintain (or cause) regression of abnormalities. To determine whether the hydralazine treatment was affecting parameters through mechanisms not associated with blood pressure control, the effects of hydralazine treatment on age-matched normotensive Wistar-Kyoto rats (WKY) also were investigated.
In addition to these structural parameters, we have also determined the effect of hydralazine treatment on the pharmacological properties of the resistance vessels, for we have shown previously that the sensitivity of the resistance vessels of the SHR to norepinephrine and to calcium is increased compared with those from WKY.15,17

Methods

Four-week-old male SHR and WKY were obtained from Møllegaard's Breeding Center, Lille Skensved, Denmark, and kept in an air-conditioned animal room (temperature, 20–21°C, lighting, 0700–1900 hr). Animals were housed three to a cage in macrolon cages (0.15 × 0.25 × 0.4 m) with sawdust bedding.

Medication

From the age of 4 weeks, half of the rats of each strain were given antihypertensive treatment consisting of the addition of hydralazine monohydrochloride (Apresoline) to their drinking water (160 mg/L tap water = 815 μM). Control animals were given tap water to drink. All rats were allowed to drink ad libitum; the water intake was 150 ml/kg/day in treated and untreated 4-week-old rats and fell to 100 to 110 ml/kg/day in the treated rats and to 50 to 75 ml/kg/day in the untreated rats at age 12 to 27 weeks. The treatment thus had a diuretic effect. Fresh solutions of the drug were prepared twice a week. Gas chromatographic analysis of the solutions showed that the hydralazine concentration decreased with a half-life of about 4 days.18 From these findings the actual dosage received by the rats was about 20 mg/kg/day initially and about 15 mg/kg/day at the time of the experiment (when they were 12–14 or 23–27 wk old).

Blood Pressure Measurement

Rats were exposed to diethylether in an open system to induce the best possible standardization of physical and mental activity before measurements. The animals were closely observed during the procedure and were found to display the characteristic stages of ether anesthesia outlined by Guedel.19 Exposure to the anesthetic was terminated at a point corresponding to Guedel’s stage III, identified by a slowing of the respiratory rate. Duration of the ether exposure never exceeded 2 minutes. This short period of anesthesia was sufficient to calm the animals but did not induce the hypotension seen with longer periods of anesthesia.20 The rat subsequently was transferred to the animal holder where pulsation in the tail artery was detected using a photoplethysmographic device (8000 series, Simonsen and Weel, Albertslund, Denmark). With the use of a non-invasive tail cuff method as described by Jespersen et al.,21 both systolic and diastolic blood pressures were determined repeatedly over 5 to 10 minutes until stable recordings were obtained, at which time the rat was fully awake, although to some degree atactic. The records obtained at this stage were taken as our estimate of blood pressure. Mean blood pressure was calculated as the sum of diastolic blood pressure plus the difference in systolic and diastolic blood pressure divided by 3. In some instances heart rate was also measured. Measurements were made between 0900 and 1500 hours. Blood pressures were measured first at the age of 7 weeks, and thereafter at regular intervals (Figure 1).

Dissection

Two days before the experiments, the final blood pressure measurement was made. Treated rats were thereafter given ordinary tap water to clear the plasma and vasculature of hydralazine. On the day of the experiment, rats were killed using CO2 and part of the proximal jejunum was rapidly excised, together with its associated vessels. As described previously, a segment (length, 1.9 ± 0.2 mm) from all groups) of a third branch off the superior mesenteric artery was isolated from this portion and mounted as a ring preparation on an isometric myograph.11,12 A double myograph was used,17 permitting two vessels to be tested and exposed simultaneously to the same solutions. The dissection and mounting were performed in standard saline (see Protocol) at room temperature.

Immediately after killing the animal, the heart was also dissected out. After removal of extraneous tissue, coagulated blood, and the atria, the heart was lightly blotted and weighed.

Solutions

Vessels were normally held relaxed in standard saline solution consisting of (mM): NaCl, 119; KCl, 4.7; NaHCO3, 25; CaCl2, 2.5; KH2PO4, 1.18; MgSO4, 1.17; ethylenediaminetetraacetic acid, 0.026; and glucose, 5.5. The potassium-saline solution was a standard saline solution in which NaCl was exchanged for KCl on an equimolar basis. The control activating solution was potassium-saline solution containing 10 μM L-norepinephrine-HCl (Sigma Chemical Co., St. Louis, MO, USA), which gives a near maximal response.12 All solutions were bubbled with 95% O2, 5% CO2 to give pH 7.4. Solutions were held at 37 °C.

![Figure 1. Development of mean (± SE) blood pressure (MBP) measured in hydralazine-treated SHR (filled circles), untreated SHR (open circles), and untreated WKY (open squares). All points for each group refer to the same animals (n = 10, treated SHR; n = 10, control SHR; n = 11, control WKY). Points for treated WKY (filled squares) are taken from Table 1.](https://hyper.ahajournals.org/doi/10.1161/01.HYP.815.13.17)
Protocol
After the samples had been mounted, the temperature of the chamber was raised to 37°C and the vessels were allowed to equilibrate for about 30 minutes with the vessel internal circumference set to give a wall tension of 0.2 N/m. At this internal circumference, the internal circumference and media thickness were measured as described previously, except that a light microscope at 340 power and bright field illumination were used. The resting tension–internal circumference characteristic was then determined, and from this the internal circumference (L_100) corresponding to a transmural pressure of 100 mm Hg was determined. The vessels were then set to the normalized internal circumference, which equals 0.9 L_100. The corresponding media thickness (m_0) was calculated from the previously determined values of internal circumference and media thickness on the assumption that the media volume remained constant. Normalized internal lumen diameter was equal to the normalized internal circumference divided by π.

Vessels were then conditioned by a series of 2-minute stimulations first with control activating solution (twice), followed by 10 μM norepinephrine in standard saline solution, potassium-saline solution, and finally, control activating solution again. The response to the last stimulation was taken as the maximum contractile response of the vessels and is the response reported in Table 3. The calcium sensitivity of the norepinephrine response was then determined. Vessels that were first depleted of available activator calcium were stimulated repetitively with norepinephrine (for 2 min every 4 min) in solutions containing increasing concentrations of calcium. Norepinephrine sensitivity was then determined in cumulative dose–response determinations; each dose was applied for 2 minutes. The norepinephrine dose–response determination was then repeated in the presence of cocaine (3 μM) to inhibit neuronal uptake of norepinephrine.

Responses have been normalized in three ways: 1) as active wall tension (i.e., the increase in wall force above resting wall force divided by twice the segment length, ΔT), 2) as active media stress (i.e., the active wall force per media cross-sectional area, equal to active wall tension divided by media thickness), and 3) as contractility or effective active pressure (i.e., as an estimate of the pressure against which the vessels would have been able to contract calculated from Δp = ΔT/(normalized internal lumen diameter/2)). Norepinephrine and calcium sensitivities are expressed in terms of pD_2 values (i.e., the negative logarithm of the dose in mol/L required to give a half-maximal response).

Statistics
The data were analyzed by using two-way analysis of variance to compare effects of treatment and age in each strain. Three-way analysis of variance to allow analysis of strain differences was also performed, but the analysis is not presented herein because, although treatment clearly was affecting the two strains of animals differently, the measurement variance of some parameters was too great to be able to demonstrate strain-treatment interaction; in such cases it was found that the analysis tended to conceal obvious effects of the treatment, particularly as regards the SHR. The analysis was performed with the generalized linear interactive modeling program GLIM, designed by a Royal Statistical Society group. Probability levels less than 0.05 were considered significant.

Results
As indicated in Figure 1 and Table 1, treatment of SHR with hydralazine prevented the blood pressure

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**Table 1. Characteristics of Rat Study Population**

<table>
<thead>
<tr>
<th>Age (wk)</th>
<th>Young adult</th>
<th>Mature</th>
<th>p&lt;sub&gt;age&lt;/sub&gt;</th>
<th>p&lt;sub&gt;sex&lt;/sub&gt;</th>
<th>p&lt;sub&gt;tm&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>13.6 ± 0.1</td>
<td>13.6 ± 0.1</td>
<td>26.7 ± 0.3</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>WKY</td>
<td>13.7 ± 0.2</td>
<td>13.7 ± 0.2</td>
<td>22.7 ± 0.1</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>88.2 ± 4.9</td>
<td>138.7 ± 5.6</td>
<td>94.5 ± 7.0</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>WKY</td>
<td>96.9 ± 4.9</td>
<td>97.9 ± 5.8</td>
<td>81.0 ± 3.3</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>291 ± 4</td>
<td>293 ± 3</td>
<td>357 ± 9</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>WKY</td>
<td>322 ± 7</td>
<td>327 ± 3</td>
<td>363 ± 5</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>434 ± 17</td>
<td>381 ± 12</td>
<td>382 ± 17</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>WKY</td>
<td>381 ± 9</td>
<td>385 ± 16</td>
<td>376 ± 5</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Number of rats is in parentheses. Two-way analysis of variance was used to determine significance of effects of treatment (p<sub>tm</sub>), age (p<sub>age</sub>), and treatment-age interaction (p<sub>sex</sub>). NS = not significant; MBP = mean blood pressure.
rise seen in the untreated SHR and kept it at or below the blood pressure level seen in the control WKY throughout the treatment period. Treatment of WKY caused a reduction of pressure only in the mature rats. The growth rate of SHR was unaffected by treatment, though the media thickness of the vessels was unaffected (see Methods); however, an inspection of the tables shows that treatment did cause a small increase in norepinephrine sensitivity of the vessels of the WKY or the calcium sensitivity of the vessels of the SHR (approximately 0.09 log unit increase in pD2). Treatment did not affect the media stress.

The sensitivity of the mesenteric resistance vessels to norepinephrine and calcium is shown in Table 4. Under control conditions, treatment had no effect on norepinephrine sensitivity. If cocaine was included in the bathing solutions to reveal the norepinephrine sensitivity of the smooth muscle cells (see Methods), however, it was found that treatment did cause a small increase in norepinephrine sensitivity of the vessels of the SHR (approximately 0.15 log unit increase in pD2). Treatment did not affect the norepinephrine sensitivity of the vessels of the WKY or the calcium sensitivity of the norepinephrine response in vessels from either SHR or WKY.

### Table 2. Heart Weight and Heart to Body Weight Ratio in Hydralazine-Treated and Untreated SHR and WKY

<table>
<thead>
<tr>
<th>Weight</th>
<th>Treated</th>
<th>Control</th>
<th>Treated</th>
<th>Control</th>
<th>p&lt;sub&gt;age&lt;/sub&gt;</th>
<th>p&lt;sub&gt;treat&lt;/sub&gt;</th>
<th>p&lt;sub&gt;age×treat&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>1.003 ± 0.018 (15)</td>
<td>1.023 ± 0.016 (15)</td>
<td>1.207 ± 0.033* (12)</td>
<td>1.364 ± 0.012 (11)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>0.949 ± 0.033* (6)</td>
<td>1.008 ± 0.023 (6)</td>
<td>1.031 ± 0.023* (5)</td>
<td>1.116 ± 0.037 (7)</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Heart/body (mg/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>3.44 ± 0.042 (15)</td>
<td>3.489 ± 0.046 (15)</td>
<td>3.377 ± 0.048* (12)</td>
<td>3.646 ± 0.052 (11)</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>2.94 ± 0.062 (6)</td>
<td>3.083 ± 0.057 (6)</td>
<td>2.837 ± 0.029 (5)</td>
<td>2.821 ± 0.11 (7)</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. Number of rats is in parentheses.

Two-way analysis of variance was used to determine significance of effects of treatment (p<sub>treat</sub>), age (p<sub>age</sub>), and treatment-age interaction (p<sub>age×treat</sub>). NS = not significant.

*p < 0.001 (significant effects of treatment where p<sub>treat</sub> < 0.05), parameters of treated rats compared by two-tailed t test with age- and strain-matched controls. t<sub>p<sub>age×treat</sub></sub> < 0.05 (significant effects of treatment where p<sub>age×treat</sub> is not significant).

**Figure 2.** (A) heart to body weight ratio (mg/g). (B) resistance vessel media to lumen ratio (% media thickness/normalized lumen diameter); (C) pressure against which resistance vessels would be able to contract when activated (effective active pressure, kPa; see Methods) for hydralazine-treated SHR (filled circles), untreated SHR (open circles), hydralazine-treated WKY (filled squares), and untreated WKY (open squares). Data obtained from Tables 2 and 3.

**Age Effects**

In addition to the age-dependent effects of treatment already noted, and apart from increases in body weight and heart weight, the only age effects seen were a 9% decrease in the heart rate of the SHR, a 10% decrease in heart to body weight ratio in the WKY, and a small increase (approximately 0.09 log unit) in the calcium sensitivity of the resistance vessels of the WKY.

**Strain Differences**

Our statistical analysis did not allow direct comparison of the parameters of SHR and WKY (see Methods); however, an inspection of the tables shows that the results are fully consistent with our previous findings showing that compared with the WKY, SHR have a greater heart to body weight ratio while their mesenteric resistance vessels have a smaller lumen, a larger media, a greater active response, a greater contractility, an increased norepinephrine sensitivity (in the presence of cocaine) and an increased...
Calcium sensitivity. More important, it should be noted that, apart from blood pressure, in no case did treatment of SHR have no effect on heart weight, although after a further 12 weeks of treatment, heart weight did not increase as much as normal. With respect to vascular structure, treatment was found to have an effect at both ages. In no instance, however, did the treatment cause any cardiac hypertrophy and increased arterial wall to lumen ratio of hypertensive persons are therefore likely to be at least partly due to the increased blood pressure, and hypotensive treatment may therefore be expected to cause regression of these abnormalities.

Structural Effects of Hypotensive Treatment

Smooth and cardiac muscle, like skeletal muscle, will respond to an increased load by an increase in the quantity of muscle. Thus, in essential hypertension, as for perhaps less complex forms of hypertension (e.g., aortic coarctation), an increased quantity of cardiac muscle and smooth muscle may be expected in the structures exposed to the increased pressure. The cardiac hypertrophy and increased arterial wall to lumen ratio of hypertensive persons are therefore likely to be at least partly due to the increased blood pressure, and hypotensive treatment may therefore be expected to cause regression of these abnormalities. However, experimental findings indicate that even though pressure reduction may be rapid, the degree and speed of regression depend on the method employed to decrease the pressure. In persons with essential hypertension, treatment with methyldopa causes regression of cardiac hypertrophy while treatment with diuretics does not appear to do so. Similarly, long-term treatment with pindolol, but not metoprolol, was

**Hypotensive Action of Hydralazine**

Although the hypotensive effect of hydralazine is well established, its mechanism of action is not known. Since the hemodynamic effect of hydralazine is to reduce the peripheral resistance, its action may be due to direct vasodilator properties. In a number of isolated preparations, direct actions of hydralazine have only been demonstrated at unphysiologically high concentrations (e.g., $10^{-4}$ M), but in other preparations, such as rat tail artery, human digit artery, and rabbit renal artery, hydralazine caused relaxation at concentrations of about 1 $\mu$M. The vasodilative effect may therefore be due to direct actions on the vascular smooth muscle, although the postsynaptic effects of hydralazine appear to be modulated both by neural mechanisms and through the endothelium.

**Table 3. Morphological and Contractile Properties of Mesenteric Resistance Vessels in Hydralazine-Treated and Untreated SHR and WKY**

<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Control</th>
<th>Treated</th>
<th>Control</th>
<th>$p_{\text{age}}$</th>
<th>$p_{\text{age}}$</th>
<th>$p_{\text{age}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>l (mm)</td>
<td>SHR</td>
<td>195.8 ± 6.2 * (15)</td>
<td>175.8 ± 5.2 (15)</td>
<td>186.1 ± 4.0 * (17)</td>
<td>179.3 ± 5.5 (16)</td>
<td>NS &lt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>m (µm)</td>
<td>SHR</td>
<td>13.53 ± 0.41 (15)</td>
<td>13.39 ± 0.69 (15)</td>
<td>11.77 ± 0.63 (17)</td>
<td>12.87 ± 0.60 (16)</td>
<td>NS NS NS</td>
<td></td>
</tr>
<tr>
<td>SHR / m</td>
<td>SHR</td>
<td>0.069 ± 0.002* (15)</td>
<td>0.076 ± 0.004 (15)</td>
<td>0.063 ± 0.003* (17)</td>
<td>0.072 ± 0.003 (16)</td>
<td>NS &lt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>SHR / m</td>
<td>WKY</td>
<td>8.61 ± 0.61 (12)</td>
<td>9.69 ± 0.81 (12)</td>
<td>10.60 ± 1.15 (10)</td>
<td>9.47 ± 0.57 (10)</td>
<td>NS NS NS</td>
<td></td>
</tr>
<tr>
<td>T (N/m)</td>
<td>SHR</td>
<td>3.89 ± 0.21 (15)</td>
<td>3.39 ± 0.17 (15)</td>
<td>3.20 ± 0.18 (17)</td>
<td>3.46 ± 0.19 (16)</td>
<td>NS NS NS</td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>4.22 ± 0.70 (12)</td>
<td>2.39 ± 0.79 (12)</td>
<td>2.69 ± 0.70 (10)</td>
<td>2.64 ± 0.11 (10)</td>
<td>NS NS NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔP (kPa)</td>
<td>SHR</td>
<td>252 ± 15 (15)</td>
<td>256 ± 15 (15)</td>
<td>280 ± 18 (17)</td>
<td>275 ± 17 (16)</td>
<td>NS NS NS</td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>288 ± 16 (12)</td>
<td>291 ± 26 (12)</td>
<td>261 ± 19 (10)</td>
<td>285 ± 17 (10)</td>
<td>NS NS NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔP / m</td>
<td>SHR</td>
<td>34.6 ± 1.9 * (15)</td>
<td>38.5 ± 1.2 (15)</td>
<td>34.3 ± 1.6 * (17)</td>
<td>38.4 ± 1.4 (16)</td>
<td>NS &lt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>WKY</td>
<td>23.5 ± 1.4 (12)</td>
<td>25.1 ± 0.8 (12)</td>
<td>25.1 ± 2.2 (10)</td>
<td>26.0 ± 1.7 (10)</td>
<td>NS NS NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± se. Number of vessels is in parentheses (1 or 2 vessels per rat). l = normalized lumen diameter; m = corresponding media thickness; $\Delta T_1$ = active wall tension response; $\Delta m_1$ = active media stress ($\Delta T_1/m_1$); $\Delta P_1$ = effective active pressure ($\Delta T_1/l_1$). Two-way analysis of variance was used to determine significance of effects of treatment ($p_{\text{age}}$), age ($p_{\text{age}}$), and treatment-age interaction ($p_{\text{age}}$). NS = not significant.

* $p_{\text{age}} < 0.05$ (significant effects of treatment where $p_{\text{age}}$ is not significant).
The response of cardiovascular structures in SHR to antihypertensive treatment shows a similar heterogeneity depending on the treatment used. Treating 24-week-old SHR for 24 weeks with a cocktail of chlorothiazide, hydralazine, and reserpine causes regression of cardiac hypertrophy and the media to lumen ratio of mesenteric resistance vessels. Conversely, vasodilators, which cause reflex action of sympathetic activity (e.g., minoxidil), do not appear to cause regression of cardiac hypertrophy. Likewise, although treating 14-week-old SHR for 10 weeks with felodipine causes regression of vascular resistance, treatment of younger SHR with this drug does not cause regression of resistance vessel structure. It is also of interest that even when drugs are effective in causing regression of cardiovascular structure the regression takes several weeks, while regression of these structures in renal resistance vessels where, according to Poiseuille's law, the 8% increase in lumen represents a 28% decrease in resistance.

Values are means ± s.e. Number of vessels is in parentheses (1 or 2 vessels per rat). Sensitivity expressed as pD2 (negative logarithm of concentration, in M), giving half-maximal response. See Table 3 for key to significance symbols.

Table 4. Sensitivity of Mesenteric Resistance Vessels of SHR and WKY to Norepinephrine (NE), Norepinephrine in the Presence of 3 μM Cocaine and Calcium (when activated with 10 μM NE)

<table>
<thead>
<tr>
<th></th>
<th>Young adult</th>
<th>Mature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Control</td>
</tr>
<tr>
<td>Cocaine-NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>6.820±0.062* (5)</td>
<td>6.617±0.056 (6)</td>
</tr>
<tr>
<td>WKY</td>
<td>6.647±0.030 (11)</td>
<td>6.551±0.041 (11)</td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR</td>
<td>4.174±0.070 (5)</td>
<td>4.110±0.037 (6)</td>
</tr>
<tr>
<td>WKY</td>
<td>3.827±0.012 (12)</td>
<td>3.774±0.034 (12)</td>
</tr>
</tbody>
</table>

Sensitivity expressed as pD2 (negative logarithm of concentration, in M), giving half-maximal response. See Table 3 for key to significance symbols.
zine-treated WKY, the lack of altered cardiovascular structure in the treated WKY could be related to their lack of altered sympathetic activity.

A third possibility, which cannot be discounted entirely, is that part of the abnormal structure developed during the 2-day period for which the hydralazine treatment was discontinued to permit measurements of the contractile ability of the resistance vessels. However, it is unlikely that blood pressure was elevated for more than a short portion of this time; thus, even though vascular synthesis can be rapid, it is unlikely that a serious artifact was introduced.

Finally, the abnormal cardiovascular structure may be genetically determined. This possibility is supported by the indications that cultured aortic cells from SHR replicate more rapidly than do those from WKY. If this is true, it would imply that the cardiovascular structure of the SHR is programmed from birth to prepare for the increased pressure that usually develops in these animals, even if the pressure does not in fact increase.

Cardiovascular Structure and Hypertension

The results of this investigation raise the question of the importance of the role of cardiovascular structure in blood pressure determination. The results show that cardiovascular structure is not an overriding determinant of blood pressure, which in the face of the large concentration of the vasodilating drug is hardly to be expected. A similar result is obtained following unclipping of two-kidney, one clip hypertensive rats, in which blood pressure is rapidly normalized despite the abnormal cardiovascular structure. Presumably there must here be a high concentration of an endogenous vasodilator present. However, as pointed out by Folkow's group, if all else is equal, an increased cardiovascular structure will contribute to an increased peripheral resistance and, hence, possibly to increased blood pressure. Although this is undoubtedly true, it does beg the question as to whether all else is equal. Since vascular structure is only a part, albeit an important part, of the system controlling peripheral resistance, increased structure does not necessarily result in increased peripheral resistance — as indeed demonstrated by the present experiments. Therefore, it may be more correct to view the altered cardiovascular structure of the SHR as a substrate on which other abnormalities may cause the hypertension normally seen in these animals.

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