Changes in Noradrenaline Sensitivity and Morphology of Arterial Resistance Vessels During Development of High Blood Pressure in Spontaneously Hypertensive Rats

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SUMMARY We have investigated whether differences seen in the pharmacological and morphological properties of mesenteric resistance vessels from spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto (WKY) controls are also present in vessels from young SHR and WKY rats in which there is little difference in blood pressure (BP). Segments of small arteries (lumen diameter 150 μm) were taken from a specific location in the mesenteric bed of 6-, 12-, and 24-week-old SHR and WKY rats, and mounted on a myograph capable of directly measuring their tension. Vessels were set to internal circumference $L_i = 0.8 L_{100}$, where $L_{100}$ was an estimate of the internal circumference the vessels would have had when relaxed in situ and under a transmural pressure of 100 mm Hg. At all ages, compared with WKY vessels, the effective lumen diameter, $L_e = L_i/\pi$, was smaller in the SHR vessels. However, media hypertrophy was seen only in vessels from 12- and 24-week-old SHRs. In physiological salt solution the noradrenaline sensitivity of all vessels was similar ($ED_{50} \approx 2.4 \mu M$). However, inhibition of neuronal uptake with cocaine revealed that at all ages the noradrenaline sensitivity of the vascular smooth muscle cells in the SHR vessels was greater than that of the cells in the WKY vessels. The results also suggested that the neuronal noradrenaline uptake was greater in the SHR vessels at all ages. The main increase in BP in the SHRs occurred between the ages of 6 week and 12 weeks. The results are therefore consistent with the hypothesis that differences in the structure of the resistance vessels are among the factors responsible for the development and maintenance of genetic hypertension. However, they point also to the possible involvement of differences in the noradrenaline sensitivity of the smooth muscle cells in the resistance vessel walls. (Hypertension 2: 664-671, 1980)

KEY WORDS • spontaneously hypertensive rat • morphology • resistance vessels • etiology

THE ELEVATED blood pressure (BP) of the adult spontaneously hypertensive rat (SHR) developed by Okamoto and Aoki1 as a model for human essential hypertension2 is associated with an increased peripheral resistance. The increased resistance may be due to a decreased caliber in the resistance vessels3,4 or to vessel rarification,3,5 but, in any case, the factors that determine the caliber of the resistance vessels must play an important part. These factors include the morphological characteristics of the vessels and the degree of their activation, which in part is controlled by the autonomic nervous system. The primary transmitter is noradrenaline, and the sensitivity of the vessels to this agonist together with their morphology are two factors of importance to our understanding of the etiology of hypertension in the SHR.

We have shown6 that, compared with vessels from Wistar-Kyoto rat (WKY) controls, third-branch mesenteric resistance vessels from 20-week-old SHRs have a smaller lumen, a thicker media, but the same in vitro noradrenaline sensitivity. Recently, however, Whall and colleagues,7 using a preparation similar to ours, have demonstrated that destruction of the nervous supply in vitro by 6-hydroxy-dopamine8 reveals that smooth muscle cell sensitivity to noradrenaline is greater in adult SHRs, but that this greater sensitivity is normally masked by a greater neuronal uptake of noradrenaline in the nerve terminals.
We initiated our present study to investigate the etiology of these parameters. Since development of increased BP in SHR occurs largely between the ages of 4 and 12 weeks,12 we have concentrated on this early period by studying mesenteric resistance vessels from 6-, 12-, and 24-week-old rats. We have examined the development of the differences in lumen diameter, smooth muscle cell noradrenaline sensitivity, and apparent differences in neuronal uptake, and have extended our previous studies13 on the development of media hypertrophy. In these experiments, the cell sensitivity and neuronal uptake have been examined by blocking the neuronal uptake mechanism with cocaine.14 The results indicate that a number of pharmacological and morphological parameters are already different in the vessels from 6-week-old SHRs and WKYs. This suggests that these differences are not the result of elevated BP, and therefore that the parameters concerned could be involved in the processes producing hypertension.

Methods

Preparation and Mounting

A 0.7 mm segment of a small (internal diameter ≤ 150 μm) artery was taken from the mesenteric bed of 6-, 12-, and 24-week-old SHR and from age-matched WKY controls. The rats were supplied by Møllegaards Avslaboratorium, L.1. Skensved, Denmark. The number of rats in each group, their BPs, body weights, and heart/body weight ratios are shown in table 1. Blood pressures were measured directly in the aorta during ketamine (Ketalar, Parke Davis, 1 mg/g) anesthesia. Technical difficulties prevented making measurements on all the rats in this investigation, but the measurements we did make were supported by further measurements kindly made by Dr. B. Ljung, AB Hässle, Gothenburg, Sweden, on rats obtained from the same supplier.

The location of the vessels selected has been described previously. For the 12- and 24-week-old rats, the vessels were third generation vessels of the superior mesenteric artery, while for the 6-week-old rats they were second generation vessels (the third generation vessels in these animals being too small to mount). The vessels were mounted on a myograph9-16 in which the vessel segments were threaded onto two wires attached, respectively, to a tension transducer and a micrometer translator. This arrangement enabled the isometric wall tension of the vessel to be directly measured while the internal circumference was controlled. The myograph was mounted on the stage of a microscope which was used to measure vessel dimensions and the thickness of the media within the vessel wall.

Solutions

The solutions used had the following compositions (in mM). Physiological salt solution (PSS) contained NaCl, 119; KCl, 4.7; KH₂PO₄, 1.18; MgSO₄, 1.17; NaHCO₃, 25; CaCl₂, 2.5; ethylenediaminetetraacetic acid (EDTA), 0.026; glucose, 5.5. During equilibration and normalization (see below), modified-PSS was circulated through the chamber in which the CaCl₂ concentration was only 1.6 mM. The Ca-free PSS had the same composition but without CaCl₂ and with 5 mM EGTA (ethyleneglycol-bis (β-aminoethylether)-N,N'-tetraacetic acid).

The cocaine-PSS had 3 μM cocaine added to the PSS. In the noradrenaline dose response experiments, noradrenaline (Hoechst) was added to PSS or cocaine-PSS in the doses indicated. All solutions were bubbled with 5% CO₂ in O₂ adjusted to pH 7.4 (with NaHCO₃) and held at 37°C.

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>6 wk</th>
<th>12 wk</th>
<th>24 wk</th>
<th>P_value</th>
<th>P_age</th>
<th>P_interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>SHR</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>10</td>
<td>10</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>SHR</td>
<td>117 ± 15</td>
<td>168 ± 6</td>
<td>201 ± 11</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td>WKY</td>
<td>110 ± 10</td>
<td>114 ± 12</td>
<td>130 ± 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>SHR</td>
<td>122 ± 11</td>
<td>291 ± 7</td>
<td>338 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WKY</td>
<td>124 ± 8</td>
<td>320 ± 8</td>
<td>370 ± 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart weight (%)</td>
<td>SHR</td>
<td>0.381 ± 0.003</td>
<td>0.330 ± 0.009</td>
<td>0.329 ± 0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (%)</td>
<td>WKY</td>
<td>0.350 ± 0.006</td>
<td>0.290 ± 0.006</td>
<td>0.281 ± 0.004</td>
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</table>

*Values show mean ± se. Significance of differences between groups is shown by P_value, P_age and P_interaction values as described in Methods section. ns = not significant.
†Blood pressure (BP) only measured in three rats per group as described in Methods section.
‡Weight of left and right ventricles.
In vitro Denervation

Vessels were denervated in vitro according to the method of Aprigliano and Hermensmeyer. After 10 minutes of treatment with 6-hydroxy-dopamine (300 \( \mu \)g/ml) while being vigorously bubbled with \( \text{N}_2 \), vessels were washed in oxygenated PSS for at least 2 hours before further experiments.

Pharmacology

The noradrenaline sensitivity of the vessels in PSS and in cocaine-PSS was determined in cumulative dose-response experiments using noradrenaline doses from 0.1 \( \mu \)M through 40 \( \mu \)M. In all cases, each dose was applied for 2 minutes, the response for each dose being taken as the active wall tension (see below) immediately before application of the new dose. Doses were changed by draining the chamber and refilling with a new solution containing the required dose.

Following normalization and the morphological measurements, noradrenaline dose-response experiments were performed with the vessels held in PSS, cocaine-PSS, and PSS. Between each dose-response experiment, the vessel was allowed to equilibrate for 15 minutes in modified-PSS. From these cumulative dose-response experiments we determined, by fitting to the logarithmic form of Hill's equation, \( \text{NA-ED}_{50} \) doses that gave half maximal responses, this parameter being taken as a measure of the vessels' noradrenaline sensitivity.

Nomenclature

Responses to the applied agonists are reported as the active wall tension, \( \Delta T \), given by \( \Delta T = \Delta F/2a \), where \( \Delta F \) is the increase in force registered by the force transducer above the force with the vessel in PSS, and \( a \) is the segment length.

In many cases (see below) noradrenaline stimulation produced phasic variations in wall tension. Here the mean wall tension over a 15-second period was used in calculating the active wall tension. Responses are also reported as effective active pressure \( \Delta p \), and active media stresses, \( \Delta \sigma \), by \( \Delta p = \Delta T/(L_i/2\pi) \), and \( \Delta \sigma = \Delta T/m_i \), where \( m_i \) is the media thickness at internal circumference \( L_i \). From Laplace's equation, \( \Delta p \) is an estimate of the pressure change which the vessel would have been able to withstand in situ for the same degree of activation and when held at the same internal circumference.

Statistics

The parameters presented in the figures and tables have been analyzed statistically using two-way analysis of variance. The significance of the differences is indicated in the legends by giving the values of \( P_{\text{strain}} \) and \( P_{\text{age}} \). These values give the probability that the differences in vessels from SHRs and WKYs, and in vessels from rats of different ages, could arise by chance. Also shown is the value of \( P_{\text{interaction}} \). A significant value of \( P_{\text{interaction}} \) indicates that the parameter concerned develops differently with age in each strain. Values are given as mean ± standard error of the mean (SE).

Results

Morphology

Following mounting, the relaxed wall tension-internal circumference characteristic of each vessel in PSS was determined. There was no indication of any residual tone in either SHR or WKY vessels, for if the characteristic was redetermined in Ca-free PSS, essentially the same characteristic was obtained. We then estimated from the characteristic obtained in PSS, using Laplace's equation, the internal circumference, \( L_{100} \), which the vessel would have had in situ when relaxed and under a transmural pressure of 100 mm Hg. Vessels were then set to an internal circumference \( L_i = 0.8 L_{100} \) for the remainder of the experiment.

The calculated effective lumen diameter corresponding to \( L_i \), given by \( L_i = L_i/\pi \), is shown in figure 1 (left). In each age group, the effective lumen diameter is seen to be 15% to 22% smaller than that of the WKY vessels. The media thickness of the vessels (taken for each vessel as the mean of measurements at 12 different locations) is shown in figure 1 (center). In the 6-week-old SHR and WKY vessels, the media thickness was the same, but in the 12- and 24-week-old vessels the media thickness of the SHR vessels was about 30% to 50% greater than that of the WKY vessels. From these measurements we have calculated the ratio between media thickness and effective lumen diameter for the vessels (fig. 1 right).

Although it is not strictly permissible to compare the morphology of the vessels between different age groups (the vessels were taken from slightly different locations, see Methods), the results suggest that the media hypertrophy seen in the vessels from the old SHRs occurs mainly between 6 and 12 weeks of age. Furthermore, the media-to-lumen ratio is seen to increase with age for the SHR vessels, but to decrease with age for the WKY vessels.

Phasic Activity

Figure 2 shows a record of a typical dose-response experiment. Although we never observed spontaneous activity with the vessels held in PSS, addition of noradrenaline frequently resulted in a response consisting of a steady tension level upon which were superimposed rhythmic tension variations with a frequency of 9 to 23 min \(^{-1} \). We term these variations "phasic activity." Such phasic activity, with an amplitude of at least 15% of the steady tension level, was seen in eight of 10 SHR vessels and in six of 10 WKY vessels from the 6-week-old rats. In the 12-week-old rats, it was seen in eight of 10 SHR vessels but in only one of 10 WKY vessels. In the 24-week-old
Effective lumen, μm

<table>
<thead>
<tr>
<th></th>
<th>WKY</th>
<th>SHR</th>
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<tr>
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<td>200</td>
<td>200</td>
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<tr>
<td>12</td>
<td>100</td>
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<tr>
<td>24</td>
<td>100</td>
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Media, μm

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<tr>
<th></th>
<th>SHR</th>
<th>WKY</th>
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<tr>
<td>6</td>
<td>15</td>
<td>15</td>
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<tr>
<td>12</td>
<td>10</td>
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Media/Lumen

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<th>WKY</th>
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<tr>
<td>6</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>12</td>
<td>0.05</td>
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<td>24</td>
<td>0.05</td>
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FIGURE 1. Left: Effective lumen diameter. Center: Media thickness. Right: Media thickness/lumen diameter at normalized internal circumference L, of arterial resistance vessels taken from 6-week (n = 10), 12-week (n = 10), and 24-week-old (n = 8) SHR (filled symbols) and WKY rats (open symbols). Bars show SE. Asterisks show significance of differences within each age group (see Methods). Analysis of variance shows: for lumen: Pstrat < 0.001; Page < 0.001; Pinteraction ns; for media: Pstrat < 0.001; Page < 0.05; Pinteraction < 0.01; for media/lumen: Pstrat < 0.01; Page is ns; Pinteraction < 0.05.

Effect of Cocaine

Cocaine was found to increase the noradrenaline sensitivity of the vessels reversibly (fig. 3). That is, in cumulative dose-response experiments, the noradrenaline dose required to give a half maximal response (NA-ED₅₀) was reversibly reduced by the addition of cocaine. Moreover, cocaine had little effect on the maximal response or on the extent of the phasic activity. The maximum effect of cocaine on the noradrenaline sensitivity was found to occur with concentrations in the range 3 to 10 μM. Cocaine alone did not produce any response even at concentrations as high as 30 μM. In all subsequent experiments using cocaine, the cocaine concentration was 3 μM.

The possible postsynaptic effects of cocaine were investigated by testing the effect of cocaine on the noradrenaline dose-response characteristics before and after the nerve endings had been destroyed in vitro by 6-hydroxy-dopamine (see Methods). In seven paired experiments, cocaine reduced the NA-ED₅₀ by a factor 8.7 ± 0.7 in SHR vessels but only by a factor 4.6 ± 0.5 in WKY vessels. Treatment with 6-hydroxy-dopamine produced similar changes in noradrenaline sensitivity, but then the effect of cocaine was greatly diminished: the shift in NA-ED₅₀ was then only by factor 1.1 ± 0.3, and there was no significant difference in this shift in SHR and WKY vessels.

FIGURE 2. Record from a dose-response experiment on 12-week-old SHR resistance vessel, showing effect of increasing dose of noradrenaline (NA) with vessel bathed in PSS. Arrows mark where solutions were changed to the next NA-concentration. Note the change in the time scale. Segment length = 0.64 mm; L_/π = 195 μm.
Noradrenaline Sensitivity

Figure 4 shows the noradrenaline dose-response characteristics of the vessels from the 24-week-old rats in the absence and presence of cocaine. The effect of cocaine is seen to be a reversible left shift in the dose-response curve. In the absence of cocaine, the dose-response curves of the SHR and WKY vessels were almost identical (NA-ED_{50} = 2.4 \mu M). The extent of the shift was greatest in the SHR vessels, however, so that in the presence of cocaine the SHR vessels had a greater sensitivity to noradrenaline (NA-ED_{50} = 0.51 \mu M) compared with the control WKY vessels (NA-ED_{50} = 0.74 \mu M).

Contractile Response

As in the vessels from the 24-week-old rats (fig. 4), the maximum noradrenaline response in both the absence and presence of cocaine of the vessels from the 6- and 12-week-old rats was obtained with a 10 \mu M noradrenaline dose, the response to 40 \mu M noradrenaline being lower. The active wall tension responses to 10 \mu M noradrenaline, \Delta T, are shown in table 3. Responses of the SHR vessels were on the average (P < 0.10) greater than those of the WKY vessels. The magnitude of the responses was not affected by cocaine.

The calculated effective active pressures and active media stresses are also shown in table 3. In each age group the effective active pressures of the SHR vessels were 30% to 60% greater than those of the correspond-
TABLE 2. Change in Noradrenaline ED₅₀ Produced by Cocaine in Resistance Vessels from 6-, 12-, and 24-week-old Spontaneously Hypertensive (SHR) and Control Wistar-Kyoto (WKY) Rats

<table>
<thead>
<tr>
<th>Rat</th>
<th>6 wk</th>
<th>12 wk</th>
<th>24 wk</th>
<th>P(strain)</th>
<th>P(age)</th>
<th>P(interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR</td>
<td>0.69 ± 0.06</td>
<td>0.71 ± 0.06</td>
<td>0.74 ± 0.06</td>
<td>&lt;0.001</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>WKY</td>
<td>0.33 ± 0.06</td>
<td>0.42 ± 0.05</td>
<td>0.46 ± 0.03</td>
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</tbody>
</table>

Based on 10 vessels in 6- and 12-week groups; seven vessels in 24-week groups.

Values show mean ± SE of ΔpD₅₀ measurements where ΔpD₅₀ is the difference in pD₅₀ = -log (ED₅₀ (M) ) of noradrenaline dose-response characteristics in the absence and presence of 3 μM cocaine.

Significance of differences between groups is shown by P(strain), P(age) and P(interaction) values as described in Methods section. ns = not significant.

Discussion

The main finding of the present study is that although the main BP elevation in the SHRs occurs between 6 and 12 weeks, small mesenteric arteries from 6-, 12-, and 24-week-old SHRs all have (compared with corresponding vessels from age-matched WKY controls): 1) a reduced lumen; 2) the same noradrenaline sensitivity under normal conditions; 3) an increased noradrenaline sensitivity in the presence of cocaine; and therefore 4) a greater shift in the noradrenaline sensitivity upon addition of cocaine. By contrast, media hypertrophy was only seen in the vessels from 12- and 24-week-old SHRs. Thus, while media hypertrophy may be the result of the increased loading caused by the increased pressure, the other differences in the SHR vessels precede the BP elevation. Since the vessels we have tested are small enough to have contributed to the peripheral resistance, the results suggest that both morphological and pharmacological factors may be involved in the development and maintenance of elevated BP in the SHR.

Morphology

The technical difficulty of making direct measurements on resistance vessels has meant that until recently their properties have had to be inferred either from perfusion experiments or from experiments on larger vessels. Perfusion studies have indicated that the vascular bed of SHRs is more reactive to adrenergic stimulation than that of WKY's. Moreover, the relaxed resistance of the SHR vascular bed is increased. An increased sensitivity has not been found, however, in preparations of individual vessels such as aorta, femoral artery, and small mesenteric resistance vessels. These results have therefore supported the hypothesis that the increased adrenergic sensitivity and increased peripheral resistance observed in perfusion experiments arise from a reduced lumen and increased media as proposed by Folkow et al. A recent morphometric investigation of SHR cerebral vessels has supported this hypothesis.

The results of the present investigation using vessels small enough to be involved in the regulation of peripheral resistance also provide supporting evidence. The increased media-to-lumen ratio that is found in the vessels from SHRs would, according to Folkow's hypothesis, explain part of the increased adrenergic reactivity seen in perfusion experiments. Moreover, even though we found no difference in the active media stress of SHR and WKY vessels, by contrast, the active media stresses in response to noradrenaline of SHR and WKY vessels were essentially the same in each age group. All these contractile characteristics (active wall tension, effective active pressure, and active media-stress) increased with age.

TABLE 3. Contractile Characteristics in Response to 10 μM Noradrenaline of Resistance Vessels from 6-, 12-, and 24-week-old Spontaneously Hypertensive (SHR) and Control Wistar-Kyoto (WKY) Rats

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>6 wk</th>
<th>12 wk</th>
<th>24 wk</th>
<th>P(strain)</th>
<th>P(age)</th>
<th>P(interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active wall tension, SHR</td>
<td>1.7 ± 0.2</td>
<td>2.5 ± 0.3</td>
<td>2.9 ± 0.3</td>
<td>ns</td>
<td>&lt;0.001</td>
<td>ns</td>
</tr>
<tr>
<td>ΔT (mN/mm)</td>
<td>WKY</td>
<td>1.4 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>2.5 ± 0.2</td>
<td></td>
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</tr>
<tr>
<td>Effective active pressure, Δp = ΔT/(L₄/2r₂) (mN/mm²)</td>
<td>SHR</td>
<td>28 ± 3</td>
<td>37 ± 4</td>
<td>39 ± 2</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WKY</td>
<td>18 ± 2</td>
<td>27 ± 3</td>
<td>27 ± 1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Active media stress, SHR</td>
<td>174 ± 18</td>
<td>186 ± 23</td>
<td>206 ± 21</td>
<td>ns</td>
<td>&lt;0.01</td>
<td>ns</td>
</tr>
<tr>
<td>Δm = (mN/mm²)</td>
<td>WKY</td>
<td>146 ± 25</td>
<td>217 ± 24</td>
<td>261 ± 19</td>
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</table>

Based on 10 vessels in 6- and 12-week groups; eight vessels in 24-week groups.

Values show mean ± SE. Significance of differences between groups is shown by P(strain), P(age) and P(interaction) values as described in Methods section. ns = not significant. L₄ = normalized internal circumference; m₁ = corresponding media thickness.
WKY vessels, this difference in vessel geometry would enable the SHR vessels to contract against a greater pressure (table 3).

Noradrenaline Sensitivity

The previous failure to find differences in the adrenergic sensitivity of isolated vessels may be the result of a failure to appreciate the extent to which the noradrenaline uptake mechanism of the nerve terminals affects this sensitivity. This uptake causes the concentration of noradrenaline in the cleft gap surrounding the alpha-receptors to be lower than that of exogenous noradrenaline in the bathing solution. Thus, the noradrenaline sensitivity of the vascular smooth muscle cells can only be determined by inhibiting this uptake. In vitro denervation has revealed an increased sensitivity of adult SHR arterial vessels such as caudal artery\(^{26, 28}\) and a preparation similar to ours.\(^{10}\) In the present investigation, cocaine was used to inhibit uptake,\(^{14}\) and our results therefore support the conclusions of these investigators that in adult rats the noradrenaline sensitivity of the vascular smooth muscle cells in the SHR vessels is greater than that of the WKY cells. Furthermore, our results extend these findings by indicating that an increased noradrenaline sensitivity is already present in the cells of vessels from 6-week-old SHRs.

The increased noradrenaline sensitivity could be the result of the increased Ca-sensitivity that we have observed in such vessels in response to noradrenaline stimulation.\(^{27}\) Such increased Ca-sensitivity has also been observed in the portal vein from SHRs\(^{38}\) and, indeed, in visceral smooth muscle from SHRs.\(^{29}\) The increased noradrenaline sensitivity could also be related to the increased degree of phasic activity that we and others\(^{10}\) have observed in the SHR vessels, although these cannot be directly related because, while the noradrenaline sensitivity of both SHR and WKY vessels increased with age, the degree of phasic activity decreased with age.

Although the use of cocaine to inhibit noradrenaline uptake has the advantage that the effect of cocaine is reversible, it has the possible disadvantage that cocaine could itself cause an increase in smooth muscle cell sensitivity.\(^{30-32}\) This does not appear to be the case, however, for the preparation we have used since we found little change in noradrenaline sensitivity in vessels in which nerves had been destroyed in vitro using 6-hydroxy-dopamine. Similarly, Marshall\(^{33}\) found no change in noradrenaline sensitivity of mesenteric arteries that had been surgically denervated. Therefore, since we did not find that cocaine potentiated the maximum response to noradrenaline or produce any response on its own, the increase in sensitivity observed upon addition of cocaine does not appear to be due to cocaine itself. Furthermore, our results with cocaine are very similar to those reported by Whall and Halpern\(^{38}\) using their denervated preparation. We therefore conclude that our results are not substantially affected by any postsynaptic influence of cocaine.

Neuronal Uptake

Whall et al.\(^{46}\) have recently measured the uptake of \(^1^H\)-noradrenaline in the nerve terminals of vessels similar to ours in 5-month-old rats and find that the uptake in SHR vessels is 44% greater than that in WKY vessels. This may be compared with our finding that the shift in NA-ED₅₀ caused by cocaine in the SHR vessels from 24-week-old rats was 60% greater than that in the corresponding WKY vessels. Therefore, our finding that similarly increased shifts are seen in the SHR vessels from 6- and 12-week-old SHRs suggests strongly that there is also in these vessels an increased uptake of noradrenaline in the nerve terminals. This increase could be due to an increased innervation, an increased number or increased effectiveness of amine pumps, or an increase in the size of the neural varicosities,\(^{5}\) and further experiments will be necessary to decide between them.

It is clear that, if this increased uptake is also present in vivo, then it would also compensate for the increased noradrenaline sensitivity of the smooth muscle cells. However, as Whall and Halpern\(^{10}\) have pointed out, the uptake mechanism is probably inoperative during adrenergic stimulation,\(^{24}\) so that the cells could be expected to respond to lower amounts of noradrenaline in SHRs compared to WKYs. Thus, the increased noradrenaline sensitivity of the cells could be a contributory factor to the increased peripheral resistance seen in vivo in the SHR.

Conclusion

Our results suggest that the different perfusion characteristics of the SHR vascular bed can be explained both by morphological differences in the resistance vessels and by differences in the noradrenaline sensitivity of the smooth muscle cells within them. These differences are present before the elevation of blood pressure, and therefore may be among the factors responsible for the development of hypertension in the SHR.

Acknowledgments

We thank Nils Nyborg for helpful discussions and Michall Stolze and Angiellelina Tepper for excellent technical assistance.

References


Stoltze and Angielina Tepper for excellent technical assistance.
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