Effects of Chronic Hypertension and Sympathetic Nerves on the Cerebral Microvasculature of Stroke-Prone Spontaneously Hypertensive Rats

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SUMMARY. The purpose of this study was to examine hemodynamic mechanisms which protect cerebral vessels against chronic hypertension, and contribute to protective effects of sympathetic nerves in the cerebral circulation. We studied stroke-prone spontaneously hypertensive rats and normotensive Wistar-Kyoto rats. At 3-4 weeks of age, all rats underwent removal of one superior cervical sympathetic ganglion. Approximately 1 year later, we cut the superior cervical sympathetic nerve contralateral to the chronic ganglionectomy and exposed pial arterioles on the cerebral cortex ipsilateral or contralateral to the chronic ganglionectomy. We measured aortic, pial arteriolar, and venous pressures with a servo-null technique, and cerebral blood flow with microspheres. Large artery resistance and small vessel resistance were calculated. During control conditions, pressure in pial arterioles was higher in stroke-prone spontaneously hypertensive rats (83 ± 6 mm Hg) (mean ± SE) than in Wistar-Kyoto rats (60 ± 3 mm Hg, P < 0.05), even though large artery resistance was almost two-fold greater in stroke-prone spontaneously hypertensive rats than in Wistar-Kyoto rats (P < 0.05). During maximal dilation produced by seizures, large artery resistance was almost three-fold higher in stroke-prone spontaneously hypertensive rats than in Wistar-Kyoto rats (P < 0.05). Small vessel resistance also was increased in stroke-prone spontaneously hypertensive rats. During seizures in stroke-prone spontaneously hypertensive rats, large artery resistance was 29% lower in chronically denervated vessels than in acutely denervated vessels (P < 0.05). Three stroke-prone spontaneously hypertensive rats had pial vessels with a “sausage string” appearance. Diameter of pial arterioles in the animals with “sausage string” vessels was greater than in stroke-prone spontaneously hypertensive rats with normal vessels (80 ± 11 vs. 56 ± 4 μm, respectively, P < 0.05). We conclude that: first, increases in large artery resistance in stroke-prone spontaneously hypertensive rats attenuate increases in cerebral microcirculatory pressure during chronic hypertension; second, structural changes in cerebral vessels account, in part, for this increased resistance; third, chronic sympathectomy reduces the structural component of resistance of large cerebral arteries in stroke-prone spontaneously hypertensive rats; and, fourth, preliminary evidence suggests that stroke-prone spontaneously hypertensive rats with “sausage string” pial arterioles may have dilation of large cerebral arteries.

vasoconstrictor responses (Folkow, 1971). Morphometric techniques have demonstrated hypertrophy of small (diameter less than 80 μm) cerebral arterioles, (Nordborg and Johansson, 1980; Hart et al., 1980; Harper and Bohlen, 1984). Structural changes in larger arteries have not been reported. Thus, one goal of this study was to determine whether structural changes in large arteries contributed to the elevated cerebral vascular resistance in animals with chronic hypertension.

Using a morphometric technique, we have found that removal of cerebral sympathetic innervation reduces hypertrophy of cerebral arterioles (Hart et al., 1980; Sadoshima et al., 1981a, 1983) and increases the incidence of stroke (Sadoshima et al., 1981a, 1983) in stroke-prone spontaneously hypertensive rats (SHRSP). A second goal of this study was to evaluate the effect of chronic sympathetic denervation on the structural component of resistance of cerebral vessels in SHRSP.

During the course of this study, we found that some SHRSP had pial arterioles with a "sausage string" appearance, as has been observed in other models of chronic hypertension (Byrom, 1954; Meyer et al., 1960; Rodda et al., 1966). The "sausage string" appearance was initially attributed to segmental "spasm" of the vessels (Byrom, 1954), and more recently to segmental vasodilatation (Auer, 1978; Kontos et al., 1981). We measured segmental resistance in these rats to determine whether large artery resistance was increased, which would be compatible with spasm, or decreased, which would indicate vasodilatation.

Methods

Surgical Preparation

We studied male and female spontaneously hypertensive stroke-prone rats (SHRSP) (n = 16) and Wistar-Kyoto (WKY) rats (n = 21) obtained from the colony at the University of Iowa. Rats were housed in temperature controlled, light-cycled quarters, with food and tap water available ad libitum. Rats underwent left or right unilateral superior cervical sympathetic ganglionectomy and contralateral sham operation between 21 and 28 days of age. Denervation produced ptosis and enophthalmus (Hoerner's syndrome) only on the denervated side.

Hoerner's syndrome was present in all rats when they were studied. At the time of study, the SHRSP weighed 218 ± 9 g and were 64 ± 0.5 weeks old and the WKY weighed 296 ± 16 g and were 57 ± 0.7 weeks old.

Animals were anesthetized (30–50 mg sodium pento-barbital/kg, ip), paralyzed (galamine triethiodide, iv), and artificially ventilated. Atropine (0.5 mg/kg, ip) was given with the anesthetic to reduce tracheal secretions. Both femoral arteries and veins were catheterized. The venous catheters were used for injection of drugs and the arterial catheters were used for withdrawal of blood and monitoring of arterial pressure.

Rats were prepared for measurement of cerebral blood flow with microspheres as described previously (Sadoshima et al., 1983). The cerebral sympathetic nerve on the side of the sham chronic sympathetic ganglionectomy was cut just inferior to the superior cervical sympathetic ganglion.

Rats were placed in a modified stereotaxic frame, and an open cranial window was prepared over the left parietal cortex, as described by Harper and Bohlen (1984). Artificial cerebrospinal fluid (Sadoshima et al., 1981b) was continuously superfused over the exposed brain and sampled at a site distant from the inlet. During control conditions and seizures, the composition of the artificial cerebrospinal fluid was: pH 7.32 ± 0.01 and 7.27 ± 0.01, respectively; Po2, 57 ± 3 and 57 ± 2 mm Hg, respectively; and PCO2, 44 ± 1 and 41 ± 1 mm Hg, respectively. The composition of the artificial cerebrospinal fluid was similar between all groups. Heparin (400 U, iv) was administered for anticoagulation.

Pressure was measured continuously in the largest pial arteriole exposed by the open window, using a servo-null pressure measuring device (model 4A, IPM Inc.). The principle of microvascular pressure measurement and development of the servo system has been described (Intaglietta et al., 1970). The tips of the pipettes used for measurement of pressure were 2–5 μm in diameter and were filled with 1.5 M NaCl (Baumbach and Heistad, 1983). The diameters of the vessels did not change after insertion of the pipets (70 ± 3 μm before and 70 ± 3 μm after insertion for 41 rats).

An image-splitting device (Vickers image-splitting eyepiece, Vickers Instruments Inc.) attached to a microscope (Olympus BHMJ series) and 10X water immersion objective (Nikon Inc.) was used to measure diameter of pial arterioles. Final magnification during measurement was approximately 80X.

Protocol

Systemic arterial pressure, pial arterial pressure, cerebral blood flow, vessel diameter, and Pco2, Po2, and pH of the artificial cerebrospinal fluid and arterial blood were measured during control and during seizures induced by bicuculline (1.0 mg/kg) to induce maximal dilatation of cerebral vessels (Meldrum and Nilsson, 1976). Large increases in blood pressure during seizures were prevented by rapid withdrawal of arterial blood. At the end of the study, animals were killed (KCl, iv), tissues were removed and weighed, and γ radiation was counted in the tissue and blood samples.

We measured flow to the right and left posterior telencephalon. The posterior telencephalon was defined as telencephalic tissue caudal to the optic chiasm. This tissue included the area of cortex exposed by the craniotomy. Preliminary experiments, in which flow to the tissue exposed by the craniotomy was measured, confirmed the findings of Baumbach and Heistad (1983) and indicated that the craniotomy and exposure to artificial cerebrospinal fluid did not affect flow.

Three SHRSP had pial arterioles with a "sausage string" appearance, as described by other investigators (Rodda et al., 1966; Byrom, 1969; Auer, 1978; Kontos et al., 1981). The micropipette used to measure pressure was inserted into the largest accessible pial arteriole, as in the other rats. Data for these animals were analyzed separately. The brain tissue from two of these animals was fixed by immersion in 10% neutral formalin, cut in 5–7 μm thick sections, stained with hematoxylin and eosin, and examined histologically for the presence of edema, hemorrhage, and infarction.

Because it was not possible to measure pial arteriolar...
and pial venous pressure in the same rats, pial venous pressure was measured in another group of rats. Six male SHRSP and five male WKY rats underwent the protocol as described above, except pressure was measured in the largest pial vein (212 ± 24 μm in SHRSP and 180 ± 16 μm in WKY) exposed under the open cranial window. In these experiments, the left atrial appendage was not catheterized and blood flow was not measured, and the rats underwent bilateral cervical sympathectomy at the time of study.

The pressure recorded in the veins of these animals was used to calculate small vessel resistance. We calculated small vessel resistance (SVR) as the difference of pressure in a small artery (PAP) and pressure in the large vein (VP), divided by the cerebral blood flow (CBF). Expressed as an equation, $SVR = (PAP - VP)/CBF$. The pressure in large veins was the same in SHRSP and WKY during control conditions (6 ± 1 mm Hg in SHRSP, 8 ± 1 mm Hg in WKY, $P > 0.05$) but different during seizures (15 ± 2 mm Hg in SHRSP, 22 ± 4 mm Hg in WKY, $P < 0.05$). Therefore, when resistance of small vessels was calculated, VP equaled 7 mm Hg during control conditions in all animals, while VP during seizures equaled 22 mm Hg for WKY and 15 mm Hg for SHRSP. We calculated large artery resistance (LAR) from the equation $LAR = (aortic pressure − PAP)/CBF$.

Branching of Cerebral Vessels in SHRSP and WKY

We determined the hierarchy of the vessels exposed by the craniotomy by counting the number of branching points between the circle of Willis and the largest pial artery exposed under the cranial window. Separate groups of SHRSP (n = 8) and WKY (n = 6) were used. The rats were anesthetized, a left parietal craniotomy was made, the area of the exposed brain was marked, Evans blue dye (approximately 12 mg) was injected iv, and the animal was killed (KCl, iv). The brain was removed and the number of arterial branching points between the circle of Willis and the area of brain exposed by the craniotomy was counted. There were 3.5 ± 0.3 branch points between the circle of Willis and the largest arteries exposed by the craniotomy in WKY and 3.2 ± 0.2 in SHRSP ($P > 0.05$). Thus, the vessels exposed by the craniotomy were of equivalent hierarchy in SHRSP and WKY rats.

Histology

The brains of two animals with “sausage string” vessels were removed and immersed in 10% formalin. Several areas of the cortex were sectioned at 5–7 μm, stained with hematoxylin and eosin, and examined microscopically. Both animals had microcystic edema, which was focal in one rat. One rat had a small area of subarachnoid hemorrhage distant from the cranial window.

Statistics

We examined effects of hypertension (SHRSP vs. WKY) and of sympathetic denervation (chronically denervated vs. chronically innervated side), and their interaction on cerebral hemodynamics using analysis of covariance (General Linear Model Procedure, SAS Institute). Blood Pco2, blood pH, and pH of artificial cerebrospinal fluid were used as covariants. Sympathetic nerves did not have a significant ($P < 0.05$) effect on most measurements of cerebral hemodynamics. Therefore, we repeated the analyses without chronic sympathetic denervation as a factor. Comparisons between means were made using the least square means procedure (SAS Institute). Null hypotheses tested were not directional except for the following: (1) because arteriolar hypotension has not been observed in SHR (see Zweifach, 1983, for review), we tested the hypothesis that chronic hypertension does not increase cerebral vascular resistance and pressure in pial arterioles, and (2) because chronic sympathetic denervation is not associated with increased minimal resistance (Rusterholz and Mueller, 1982, Sadoshima et al., 1983) or augments hyper trophy (Bevan and Tsuru, 1979; Hart et al., 1980; Bevan and Tsuru, 1981), chronic sympathetic denervation would not reduce cerebral vascular resistance during control or maximal dilation. Null hypotheses were rejected when the probability that they were correct (by random chance) was less than 5%.

Results

Chronic Hypertension

The SHRSP and WKY used in this study were drawn from a population of 24 hypertensive and 26 normotensive rats. Some animals were not used because of bleeding into the craniotomy, inability to survive surgery, or other technical problems. Systolic blood pressure, determined by tail plethysmography, of the rats studied was: WKY = 104 ± 3 mm Hg, SHRSP = 182 ± 5 mm Hg ($P < 0.05$). The rats averaged 51 (WKY) and 60 (SHRSP) weeks of age at the time of measurement of arterial pressure.

At the time of terminal study, intra-arterial pressure was higher in the SHRSP than in the WKY rats (Table 1). Pial arteriolar diameter was less in SHRSP than in WKY ($54 ± 5 vs. 77 ± 4 μm$, respectively, $P < 0.05$). The gradient in pressure between the aorta and pial vasculature was greater in SHRSP than in WKY (Table 1). Thus, although aortic pressure was 58 mm Hg higher in SHRSP than in WKY, pial arteriolar pressure was only 23 mm Hg higher.

Cerebral blood flow was similar in SHRSP and WKY during control conditions (Table 1). Thus, resistance of large cerebral arteries during control conditions was higher in SHRSP than in WKY (Fig. 1). During seizures, cerebral blood flow was less in SHRSP than WKY (Table 1) and resistance of large arteries was greater in SHRSP than WKY (Fig. 1). The "active" component of large artery resistance (equal to resistance during control conditions minus resistance during seizures) was higher in SHRSP than in WKY ($1.0 ± 0.3$ vs. $0.5 ± 0.1$ mm Hg/ml per min × 100 g, respectively, $P < 0.05$). Small cerebral vessel resistance during control conditions, and maximal dilation was increased in rats with chronic hypertension (Fig. 2). These differences also achieved statistical significance if venous pressure was assumed to be zero.

Effect of Chronic Sympathetic Denervation

During control conditions, chronic denervation had no effect on resistance of large cerebral arteries (Table 2). Large artery resistance tended to be higher under control conditions in the innervated group, presumably because arterial pressure was higher.
TABLE 1
Cerebral Hemodynamics in SHRSP and WKY*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Seizures</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>WKY (n = 21)</td>
<td>SHRSP (n = 16)</td>
</tr>
<tr>
<td>Mean aortic pressure</td>
<td>98 ± 4</td>
<td>156 ± 7†</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pial arteriolar pressure</td>
<td>60 ± 3</td>
<td>83 ± 6†</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure difference</td>
<td>38 ± 2</td>
<td>74 ± 4†</td>
</tr>
<tr>
<td>(aortic-pial arteriole)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>58 ± 5</td>
<td>60 ± 7</td>
</tr>
<tr>
<td>(ml/min x 100 g)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = number of animals.
* Values are mean ± se.
† Significantly different from value for WKY (P < 0.05).

During maximal dilation, resistance of chronically denervated large cerebral arteries in SHRSP was 29% lower than in chronically innervated vessels (Table 3) (P < 0.05). Denervation did not affect resistance of small cerebral vessels during control conditions or maximal dilatation (Tables 2 and 3).

**"Sausage String"**

Three of the SHRSP in this study had marked variation in caliber of some pial arterioles. There were areas of focal dilation and/or constriction, giving a small-length of an arteriole the appearance of a string of sausages.

Aortic pressure of the SHRSP with irregular arterioles was similar to aortic pressure in the other SHRSP, but pressure in pial arterioles was significantly elevated in the "sausage string" group (Fig. 3). The diameter of the segment of vessel near the site where the micropipette was inserted was higher (P < 0.05) in the "sausage string" group (80 ± 11 μm) than in SHRSP with normal vessels (56 ± 4 μm). Resistance of large cerebral arteries tended to be lower in the "sausage string" group under control conditions (0.9 ± 0.3 mm Hg/ml per min x 100 g) than in SHRSP with normal vessels (1.5 ± 0.2 mm Hg/ml per min x 100 g), but the difference did not achieve statistical significance (P > 0.05). During maximal dilation produced by a seizure, there was a significant (P < 0.05) reduction in the resistance of large cerebral arteries in SHRSP with normal vessels (1.0 ± 0.3 mm Hg/ml per min x 100 g), but...
TABLE 2
Effect of Chronic Sympathetic Denervation on Cerebral Hemodynamics: Control Conditions*

<table>
<thead>
<tr>
<th></th>
<th>WKY Innervated (n = 11)</th>
<th>WKY Denervated (n = 10)</th>
<th>SHRSP Innervated (n = 6)</th>
<th>SHRSP Denervated (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>95 ± 7</td>
<td>100 ± 5</td>
<td>141 ± 9</td>
<td>165 ± 9</td>
</tr>
<tr>
<td>Mean pial pressure (mm Hg)</td>
<td>60 ± 5</td>
<td>60 ± 5</td>
<td>75 ± 10</td>
<td>86 ± 7</td>
</tr>
<tr>
<td>Cerebral blood flow (ml/min x 100 g)</td>
<td>55 ± 6</td>
<td>61 ± 10</td>
<td>59 ± 13</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>Large artery resistance (mm Hg/ml per min x 100 g)</td>
<td>0.71 ± 0.09</td>
<td>0.84 ± 0.13</td>
<td>1.36 ± 0.24</td>
<td>1.58 ± 0.31</td>
</tr>
<tr>
<td>Small vessel resistance (mm Hg/ml per min x 100 g)</td>
<td>1.15 ± 0.23</td>
<td>1.05 ± 0.17</td>
<td>1.36 ± 0.33</td>
<td>1.54 ± 0.30</td>
</tr>
<tr>
<td>Blood gases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
<td>107 ± 8</td>
<td>109 ± 12</td>
<td>148 ± 11</td>
<td>138 ± 13</td>
</tr>
<tr>
<td>Pco2 (mm Hg)</td>
<td>36 ± 1</td>
<td>36 ± 3</td>
<td>32 ± 1</td>
<td>36 ± 1</td>
</tr>
<tr>
<td>pH</td>
<td>7.37 ± 0.02</td>
<td>7.34 ± 0.02</td>
<td>7.34 ± 0.03</td>
<td>7.39 ± 0.03</td>
</tr>
</tbody>
</table>

n = number of animals.
* Values are mean ± SE.
† For comparisons between SHRSP and WKY, see Figures 1 and 2 and Table 1.

Discussion

There were four major findings in this study. First, an increase in resistance of large cerebral arteries in SHRSP results in attenuation of elevated pressure in pial arterioles. Second, resistance during maximal dilatation is increased in large cerebral arteries and small cerebral vessels in SHRSP, which indicates an increased structural component of resistance. Third, removal of sympathetic nerves reduces the structural component of resistance of large cerebral arteries. Fourth, preliminary observations suggest that large cerebral vessels are dilated, perhaps maximally, in SHRSP with pial vessels that have a “sausage string” appearance.

Several aspects of this study warrant discussion. We will discuss the methods used in the experiments, the effect of chronic hypertension on the cerebral circulation, and the trophic effect of nerves on the cerebral vasculature.

TABLE 3
Effect of Chronic Sympathetic Denervation on Cerebral Hemodynamics: Maximal Dilation during Seizures*

<table>
<thead>
<tr>
<th></th>
<th>WKY Innervated (n = 11)</th>
<th>WKY Denervated (n = 6)</th>
<th>SHRSP Innervated (n = 6)</th>
<th>SHRSP Denervated (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>117 ± 8</td>
<td>118 ± 7</td>
<td>161 ± 7</td>
<td>179 ± 10</td>
</tr>
<tr>
<td>Mean pial pressure (mm Hg)</td>
<td>63 ± 6</td>
<td>70 ± 2</td>
<td>66 ± 9</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>Cerebral blood flow (ml/min x 100 g)</td>
<td>284 ± 34</td>
<td>349 ± 29</td>
<td>175 ± 36</td>
<td>236 ± 37</td>
</tr>
<tr>
<td>Large artery resistance (mm Hg/ml per min x 100 g)</td>
<td>0.23 ± 0.04</td>
<td>0.15 ± 0.02</td>
<td>0.69 ± 0.19</td>
<td>0.49 ± 0.08†</td>
</tr>
<tr>
<td>Small vessel resistance (mm Hg/ml per min x 100 g)</td>
<td>0.15 ± 0.02</td>
<td>0.14 ± 0.02</td>
<td>0.32 ± 0.06</td>
<td>0.31 ± 0.07</td>
</tr>
<tr>
<td>Blood gases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
<td>96 ± 9</td>
<td>98 ± 7</td>
<td>156 ± 17</td>
<td>144 ± 22</td>
</tr>
<tr>
<td>Pco2 (mm Hg)</td>
<td>35 ± 2</td>
<td>38 ± 3</td>
<td>24 ± 2</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>pH</td>
<td>7.25 ± 0.02</td>
<td>7.26 ± 0.03</td>
<td>7.16 ± 0.03</td>
<td>7.30 ± 0.06</td>
</tr>
</tbody>
</table>

n = number of animals.
* Values are mean ± SE.
† For comparisons between WKY and SHRSP, see Figures 1 and 2 and Table 1.
‡ Significantly different from value for innervated SHRSP (P < 0.05).
Pressure and Reed, 1983). Also, conclusions about the resistance of pressure in cerebral veins (Shulman, 1965; Wiig 1979; Hoffman et al., 1981, 1982; Sadoshima et al., 1983) are near normal in most vascular beds (Hertel et al., 1978; Zweifach et al., 1981; Harper and Bohlen, 1984). It has been demonstrated previously that cerebral precapillary arteriolar pressure (Harper and Bohlen, 1984) and cerebral blood flow (Hoffman et al., 1982; Sadoshima et al., 1983) are near normal in SHR, which implies that resistance of large cerebral arteries is increased in SHR. In the present study, simultaneous measurements of cerebral blood flow and the difference in pressure between the aorta and pial vessels demonstrated that, during control conditions, resistance of large cerebral arteries of SHRSP is elevated.

The increased resistance of large cerebral arteries could result from a number of influences. First, Baumbach and Heistad (1983) found that sympathetic stimulation increases resistance of large, but not small, cerebral arteries. However, even if sympathetic tone is increased in SHRSP (Judy et al., 1976; Mueller and Ertel, 1983), it is an unlikely explanation of our observation of elevated large artery resistance, because the cerebral vessels were sympathetically denervated, either chronically or acutely. Second, although extracerebral vessels are influenced by a variety of humoral influences, brain vessels are, at most, weakly affected by such influences, because the blood brain barrier prevents humoral agents from reaching their receptor sites on vascular muscle. Third, the most likely explanation for elevated resistance of large cerebral arteries in SHRSP is that the structural component of resistance is increased. Increased resistance of large arteries of SHRSP during maximal dilation indicates that the large cerebral arteries have undergone a structural change. Other studies suggest that medial hypertrophy accounts for this structural change in the cerebral vessels of SHRSP (Hart et al., 1980) and SHR (Harper and Bohlen, 1984).

One consequence of structural changes is that vascular reactivity is exaggerated (Folkow, 1971). Consistent with our observation of a structural change, we found that the “active” (nonstructural) component of cerebral vascular resistance was elevated in SHRSP. Therefore, we conclude that the elevated resistance of large cerebral arteries in SHRSP observed during control conditions is the
result of an increased structural and active component of resistance. The mechanism of the increased active component is unclear, but may simply be secondary to augmentation of vasoconstrictor responses by the structural change.

Despite elevated resistance of large arteries in SHR, pressure in the microcirculation was elevated. Small vessel resistance also was elevated in SHRS. The major cause of elevated small vessel resistance probably is an increase in the structural component of resistance, as demonstrated by the increased resistance during maximal dilation.

The elevated pressure in the cerebral microcirculation in SHRS indicates that brain vessels are not completely protected against systemic hypertension. Three SHRS had pial vessels with a "sausage string" appearance, which may be a consequence of this incomplete protection. This abnormal vascular pattern has been observed in pial arterioles in animals with chronic hypertension (Byrom, 1954; Meyer et al., 1960; Rodda et al., 1966). It is not known whether this pattern represents focal dilation (Auer, 1978; Kontos et al., 1981), constriction (Meyer et al., 1960; Rodda et al., 1966), or both (Byrom, 1954).

Local mechanisms that lead to the irregular shape of the arterioles are not clear. Because one would expect relatively uniform pressure in adjacent arteriolar segments, the irregular pattern observed in the "sausage string" vessels probably is a consequence of non-uniformity in responses of the vessel wall to elevation of pressure. In acute hypertension, uniform dilation occurs in most, but not all, pial arterioles (Kontos et al., 1981). The arterioles that were not uniformly dilated had a "sausage string" appearance. These observations are consistent with the suggestion that the "sausage string" appearance of vessels results from differential sensitivity of various segments of the vessel wall to elevation of intravascular pressure.

Our preliminary observations are the first measurements of pial arteriolar diameter or hemodynamics in animals with chronic hypertension and pial vessels with a "sausage string" appearance. The finding of increased diameter and pressure in pial arterioles of SHRS with "sausage string" vessels compared to SHRS with normal pial vessels suggests that the large arteries were dilated in the former animals. However, elevated resistance of small vessels also may have contributed to the increased pressure in pial vessels in the "sausage string" group. Thus, our observations suggest (but are not conclusive) that dilation of large arteries occurs in animals with chronic hypertension and a "sausage string" appearing vessels.

Trophic Effect of Sympathetic Nerves

It has been suggested that sympathetic nerves have a trophic effect on blood vessels (Bevan, 1975; Fronk et al., 1978; Hart et al., 1980; Bevan and Tsuru, 1981). Removal of the sympathetic innervation to cerebral vessels in 1-month-old SHRS results in (1) morphometric evidence of a reduction in vascular hypertrophy (Hart et al., 1980; Sadoshima et al., 1981a, 1983), (2) reduction in the pressure at which there is "breakthrough" of autoregulation of cerebral blood flow (Sadoshima et al., 1983), and (3) cerebral hemorrhage and infarction occurring primarily on the denervated side (Sadoshima et al., 1981a; Sadoshima et al., 1983), but (4) no decrease in resistance at maximal dilation (Sadoshima et al., 1983). In this study, we found a reduction in resistance of chronically denervated vs. innervated large arteries at maximal dilation in SHRS. There are a number of possible explanations for the discrepancy between this study and the previous one (Sadoshima et al., 1983). First, chronic sympathetic denervation increases the stiffness of blood vessels in vitro (Bevan and Tsuru, 1979). This effect might be expected to increase resistance at maximal dilation. Thus, chronic sympathetic denervation might not affect minimal resistance if the increase in stiffness offsets the reduction in vessel growth. We waited a year after denervation to study the animals, which may have resulted in a greater effect of denervation on the growth of vessels (compare Hart et al., 1980, to Sadoshima et al., 1981a and 1983) than on stiffness. Second, we examined segmental resistance at maximal dilation. This was important, as removal of sympathetic nerves did not affect the structural component of resistance of small cerebral vessels. Therefore, we conclude that sympathetic nerves affect the structural component of resistance of large cerebral vessels in SHRS, and this effect is detectable when measured with hemodynamic techniques.

Our finding of reduced resistance during maximal dilation of chronically denervated vessels is consistent with the hypothesis that the lumen of the denervated vessels was larger during maximal relaxation. Although this could have been a consequence of reduced vascular hypertrophy (Folkow, 1971), there are alternative explanations. For example, chronically denervated vessels might have a lower resistance when made passive because they are less stiff than innervated vessels. However, it has been proposed that chronic sympathetic denervation increases rather than decreases the passive stiffness of vessels (Bevan and Tsuru, 1979). Thus, increased stiffness of denervated vessels during maximal relaxation is an unlikely explanation of our results. Second, rarefaction of vessels can account for increased minimal vascular resistance. Because the effect of chronic sympathetic denervation on vascular rarefaction has not been evaluated, this explanation of our results cannot be ruled out.

If denervation results in attenuation of vascular hypertrophy (Hart et al., 1980; Bevan and Tsuru, 1981; Sadoshima et al., 1981a, 1983), then tension in chronically denervated pial vessels would be elevated if pressure in those vessels were greater than
or similar to that of chronically innervated vessels. We found, during control conditions, that pressure in denervated pial vessels was not different (when taking systemic pressure into account) from that in chronically innervated pial vessels. Thus, chronic denervation may result in increased wall tension. We speculate that this increased wall tension may contribute to the predisposition to stroke in SHRSP after chronic sympathetic denervation.

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References


Heistad DD, Marcus ML (1979) Effect of sympathetic stimulation on permeability of the blood-brain barrier to albumin during acute hypertension in cats. Circ Res 45: 331-338


Strandgaard S, Olesen J, Skinhoj E, Lassen NA (1973) Auto-

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