Antihypertensive Drug Therapy Prevents Cerebral Microvascular Abnormalities in Hypertensive Rats

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Studies were performed on anesthetized 16-18 week old normotensive Wistar-Kyoto rats, spontaneously hypertensive rats, and Goldblatt two-kidney one clip renal hypertensive rats, treated from age 4-5 weeks with an oral antihypertensive regimen consisting of hydralazine, reserpine, and chlorothiazide. Measurements of flow and intravascular pressure in the cerebral microvasculature were made via a constantly suffused open cranial window using video microscopy. A significant upward shift was seen in the pressure range for cerebral blood flow autoregulation in both groups of untreated hypertensive animals. Following treatment, the autoregulatory range in both hypertensive models was restored to a level nearly identical to control. The prevention of this shift in treated animals was due primarily to the prevention of structural microvascular adaptations that occur in untreated hypertensive animals. By preventing elevations in microvascular pressure, treatment may have eliminated the major stimulus for development of hypertrophy in resistance vessels. However, a persistent increment of arteriolar wall mass in treated spontaneously hypertensive rats may represent a hyperplastic response not influenced by treatment. Likewise, a persistent constriction of the smallest arterioles in treated renal hypertensive rats may represent a differential sensitivity of microvessels to circulating vasoactive agents. It appears that treatment initiated in the prehypertensive state, or before significant sustained hypertension has occurred, can markedly reduce the cerebrovascular morbidity associated with two different forms of hypertension. (Circulation Research 1987;60:229-237)

Structural and functional adaptations of the cerebral vasculature during progression of hypertension are well established. These adaptations include an upward shift in the pressure range for cerebral blood flow (CBF) autoregulation, microvascular hypertrophy and resting constriction, and protection of the exchange vasculature from elevated blood pressure. The primary consequence of these adaptations is the maintenance of normal CBF in hypertensive individuals such that the potential for edema and encephalopathy is minimized. However, the existence of elevated transmural pressure in cerebral arterioles greatly increases the risk of stroke.

The efficacy of antihypertensive therapy in preventing the cardiovascular morbidity associated with established essential hypertension has been demonstrated. Ultrastructural and morphometric studies of aortic and intrarenal vessels in age-matched spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto (WKY) controls showed expansions of the subendothelial space, medial thickening of the aorta, and an increase in external to luminal diameter ratios and wall thickness of intrarenal vessels in the SHR. These lesions were prevented by antihypertensive treatment initiated before the onset of hypertension, though discontinuation of therapy resulted in reestablishment of vascular lesions in SHR. Studies of the response of CBF autoregulation to hypertensive therapy in aged (24-month old) SHR indicated that maintenance of constant CBF was significantly improved following 10 weeks of antihypertensive therapy. Following antihypertensive treatment with intravenous diazoxide and dihydralazine in both SHR and renal hypertensive rats (RHR), the CBF autoregulatory range was restored to normal. While both studies provided valuable information regarding the autoregulation of CBF following antihypertensive treatment, neither addressed the effects of treatment on cerebral microvascular structure/function changes.

In the present study, antihypertensive treatment was initiated prior to the development of hypertension in both SHR and RHR to determine if there are structural or functional microvascular abnormalities that may develop independently of an elevation in mean arterial pressure. Thus, if there are significant abnormalities present in treated hypertensive animals that have never experienced elevated pressure, then these persistent abnormalities might be attributed to fundamental differences in the pathogenesis for a particular hypertensive model. Also investigated were the adaptations to hypertension in the cerebral vasculature of renal hypertensive rats, to determine if a different mechanism of hypertension would result in markedly different structural/functional adaptations.

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Materials and Methods

Surgical Preparation

Animals (Taconic Farms, Germantown, NY) were anesthetized with a saline solution of Inactin, a sodium salt of ethyl-(1-methylpropyl)-malonyl-thio-urea (Byk Gulden Konstanz, West Germany; 10 mg/100 g body weight, i.p.), with supplemental injections (2 mg/100 g body weight) given as needed, though rarely necessary. Inactin was used because it provides more consistent maintenance of mean arterial blood pressure than other anesthetics, such as chloralose, urethane, and pentobarbital. The trachea was intubated to ensure a patent airway, and the femoral artery and vein were cannulated for measurement of systemic arterial blood pressure and drug injection, respectively. The rectal temperature was maintained at 37 ± 1°C with a heating mat.

Surgical procedures consisted of securing the head in a stereotaxic device followed by a mid sagittal incision through the scalp, using thermocautery and topically applied ferric chloride solution to minimize cautery. An approximately 4 × 7 mm area of parietal calvarium was circumscribed by an air-cooled burr held in an electric drill (Dremel Moto-Tool). The bone plate was removed with a periosteal elevator and forceps. The dura mater was reflected, ideally along avascular lines, using a dural hook and small ophthalmic scissors. The exposed cortical surface microvasculature was then bathed with a bicarbonate-buffered physiological solution (for specific composition, see Harper et al) having the following characteristics after gas equilibration: Po2, 40-45 mm Hg; Pco2, 38-43 mm Hg; pH, 7.35-7.45. The bathing fluid was suffused over the brain surface at a rate of 3-4 ml/min such that the pool of fluid was constantly replenished at least 2 to 3 times per minute and the fluid temperature remained at 37 ± 1°C. The aforementioned values of Po2, Pco2, and pH were found to be stable during pilot studies lasting 2-3 hours, the average duration of a typical experiment. Po2 measurements were made with microelectrodes, and vasoconstriction ensued when the CSF pool was allowed to stagnate with attendant increases in Pco2 and pH, and decreases in Po2. Therefore, as long as gas and fluid delivery was maintained at levels consistent with those of the pilot studies, artificial CSF gas tensions at the level of the cerebral cortex were presumed to be fairly constant.5

An Aus Jena microscope with Nikon water immersion lenses (10 ×, n.a. = 0.22; 20 ×, n.a. = 0.33) was used to provide images for a Cohu Electronics 4400 video camera and a Panasonic TV monitor. All images were recorded on video cassettes with a Panasonic NV-8320 video recorder so that measurements could be made after the experiment. A timer superimposed on the video screen allowed for synchronization of video tape and chart recorder data. Water immersion lenses were used to avoid resolution problems caused by the curved air-water interface of the suffusion solution. Illumination of the brain surface was provided by a one-eighth inch fiber-optic bundle oriented at a 20–30° angle to the optical plane of the microscope, and connected to a Martin Instruments light source. Infrared light was filtered such that light from the fiber-optic bundle had no thermal effect on the stationary fluid pool.

In a typical experiment, the animal was allowed to recover for a minimum of 30 minutes after surgery was completed. Evidence of damage (e.g., petechial hemorrhage) to 5% or more of the tissue resulted in termination of the experiment before data acquisition. If none of the microvessels dilated by a minimum of 50% when adenosine (10^-3 M) was topically applied, the preparation was discarded. Given the heterogeneity of blood flow in the brain, some vessels may dilate more than others following adenosine application; however, the absence of dilation in all vessels is a clear indication that the autoregulatory mechanism is disrupted and the vasculature is pressure-passive.

Categorization of cerebral vessels into groups by hierarchical branching pattern is difficult because of the extensive collateralization of the proximal vasculature. In spite of these conditions, first-order arterioles (1A) are defined as the largest vessels that enter the operative field from directly beneath the skull margin. Second-order arterioles (2A) are defined as those vessels which branch from 1A vessels at nearly right angles and, likewise, third-order arterioles (3A) branch at nearly right angles from 2A vessels. Fourth-order arterioles (4A) branch similarly from the 3A and either directly perfuse surface capillaries or dive into the cortical parenchyma. Although there are clearly exceptions to this method of ordering (e.g., vessels of 3A diameter branching directly from large 1As) it is nevertheless useful for grouping the vessels in approximately equal categories of diameter and branch order. In most cases, 4A vessels are the immediate precursors to either capillaries or short precapillary vessels. A photographic description of this procedure has been published previously.6

Measurements of Microvascular Pressures, Diameter, and Blood Flow

Microvascular pressures were measured in all orders of arterioles and venules using a servo-nulling pressure measurement system, employing glass pipette microelectrodes with sharpened tip diameters of 1–1.5 μm. Electrodes are attached to a fluid-filled tubing system containing 2 M NaCl. When electrode tips are immersed in physiological solutions, an interface develops between the 2 M NaCl and the 0.15 M NaCl. When a pressure greater than “zero” (atmospheric) is applied to the tip, the saline interface is displaced, thereby altering pipette resistance. The system generates a precise counter pressure to restore the saline interface, and this counter pressure appears on the chart record as the equivalent of microvascular pressure. This system was calibrated before and after each experiment.

Vessel diameters were measured using a video-splitting device (IPM Model 907) that employs digitized images of videotaped experimental records. This system was calibrated at a constant magnification (700 ×)
with a Bausch and Lomb stage micrometer. The range of measurement and linearity of output were confirmed with the micrometer. Repeated measurements of a particular steady-state microvessel were made by using an analog-to-digital conversion program that sampled diameter measurements every second and computed average diameter over 1 minute. The average of these determinations was recorded as the diameter for that particular vessel and perturbation. Since the largest source of variability exists between vessels and/or animals, repeated measurements on a single vessel would improve the reliability of that particular measurement without adversely affecting the variability of the entire sample. Wall area was calculated as the difference between the whole vessel cross-sectional area and luminal cross-sectional area. External vessel wall boundaries are particularly easy to discern in the brain, given the high contrast between vessel wall substance and underlying brain tissue. Internal wall boundaries are evident from the rough endothelial surface of the vessels. Passive diameters were measured following topical application of adenosine (10^{-3} M). Adenosine at this concentration produces increases in vessel diameter (67% above control) similar to those seen in paired studies with topical application of nitroprusside (75% increase), nitroglycerin (61% increase), and inhalation of 5% CO₂ (73% increase). However, nitroglycerin and nitroprusside generally produced hypotensive side effects, making their routine experimental use difficult. Carbon dioxide inhalation produced variations in respiratory movement that complicated measurement of vessel diameter. Thus, adenosine emerged as the vasodilator of choice. All vessel measurements were normalized following blood pressure reduction (typically 60-90 seconds following perturbation), diameter 10 mm Hg were induced by controlled hemorrhage from the femoral artery to a heparinized reservoir. When the microvascular responses had reached a new steady state following blood pressure reduction (typically 60–90 seconds following perturbation), diameter

### Induction of Renal Hypertension

Renal hypertensive rats were developed from normotensive Wistar-Kyoto rats at age 4–6 weeks. The use of WKY is necessary since the RHR were compared to SHR, and the SHR and WKY were originally developed from the same parent strain. Solid silver clips (approximately 0.2 mm diameter) were placed around the right renal artery in experimental rats. The left kidney remained intact. Fourteen of 20 (70%) of these rats (untreated) developed sustained hypertension within a week following the operative procedure. In sham-operated controls, the same surgical procedure was followed, except that the clip was placed around the right renal artery, and then removed before the midline incision was closed. Thus, it was impossible to discern from postoperative inspection which rats were normal and which were hypertensive. The induction of hypertension of 6-week-old rats corresponds roughly to the onset of hypertension in SHR, so all subsequent comparisons were made in rats that had been hypertensive for approximately equal durations (confirmed by indirect blood pressure measurement protocol described below).

### Antihypertensive Treatment Regimen

The treatment consisted of the following doses added to the drinking water: hydralazine, 10 mg/kg/day; reserpine, 0.20 mg/kg/day; and chlorothiazide, 200 mg/kg/day. These doses produced the desired blood pressure responses within 2 weeks in pilot studies. Solutions were prepared fresh and added to the drinking water every evening in the desired doses.

All animals (treated and untreated) were housed in air-conditioned quarters with light time control and fed standard rat chow. The amount of food and water consumed was measured daily, and body weight and blood pressure were measured 3 times weekly. Blood pressure measurements were made at the same time of day using a tail cuff occlusion apparatus (Narco Biosystems).

### General Experimental Protocol

All animals were allowed to recover for a minimum of 30 minutes following surgery. Each experiment began with resting measurements of microvascular pressure, diameter, and blood flow velocity in a number of randomly selected vessels. Following this procedure, autoregulatory adjustments to changes in perfusion pressure were derived from diameter and blood flow velocity in 1A vessels. Blood pressure decreases of 10–20 mm Hg were induced by controlled hemorrhage from the femoral artery to a heparinized reservoir. When the microvascular responses had reached a new steady state following blood pressure reduction (typically 60–90 seconds following perturbation), diameter.
Table 1. Selected Physiologic Data on Treated (T) and Untreated (U) Wistar-Kyoto (WKY), Spontaneously Hypertensive (SHR), and Renal Hypertensive (RHR) Rats

<table>
<thead>
<tr>
<th></th>
<th>WKY-U</th>
<th>WKY-T</th>
<th>SHR-U</th>
<th>SHR-T</th>
<th>RHR-U</th>
<th>RHR-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of animals</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Body wt (g)</td>
<td>278±12</td>
<td>289±9</td>
<td>246±13</td>
<td>237±8</td>
<td>261±6</td>
<td>273±9</td>
</tr>
<tr>
<td>Duration of hypertension (days)</td>
<td>…</td>
<td>…</td>
<td>85±3</td>
<td>…</td>
<td>84±4</td>
<td>…</td>
</tr>
<tr>
<td>Duration of treatment (days)</td>
<td>…</td>
<td>79±2</td>
<td>…</td>
<td>87±6</td>
<td>…</td>
<td>93±2</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>120±4</td>
<td>104±6*</td>
<td>176±8</td>
<td>109±7*</td>
<td>161±11</td>
<td>111±5*</td>
</tr>
</tbody>
</table>

All values are mean ± SEM.
*p<0.05 vs. untreated; unpaired t test.

and flow velocity were measured. Blood volume was restored in approximately the same manner as it was depleted, i.e., 10–20 mm Hg pressure increments. No mechanical hysteresis was detected in any measurements obtained during blood pressure reduction and restoration over a range of 40–260 mm Hg. Vasodilator drugs were not used to lower arterial pressure because of the possibility of direct vascular effects by the drugs. Blood pressure elevations were obtained via intravenous infusion of a freshly prepared, pH-buffered norepinephrine solution (0.28 to 1.275 μg/min, depending on the level of hypertension desired). Endogenous and infused norepinephrine do not influence intact cerebral vessels because topically applied norepinephrine at concentrations of 10⁻⁸ M to 10⁻³ M has no direct effect on vessel dimensions. To verify that norepinephrine had little or no effect on the cerebral microvessels, as described in a previous study, arterial pressure was elevated by a continuous norepinephrine infusion and then lowered to control levels by hemorrhage during the norepinephrine infusion. The diameters of arterioles at rest and during the combined norepinephrine-hemorrhage protocol were equal as long as blood pressure was identical in both circumstances.

At the end of each experiment, animals were killed by overdose of sodium pentobarbital, followed by intravenous potassium chloride.

Statistical Analysis

Data are reported as mean ± standard error. Comparisons between two means were made by appropriate t test. Comparisons between more than two means were evaluated initially by analysis of variance to detect significant differences among the group means. Multiple comparisons were then executed as necessary using Duncan’s multiple range test. Probability values less than 0.05 were considered to indicate a significant difference between means.

Results

A total of 55 rats were successfully studied in 6 separate treatment groups: treated WKY (WKY-T), SHR (SHR-T), and RHR (RHR-T); and untreated WKY (WKY-U), SHR (SHR-U), and RHR (RHR-U). Relevant physiologic data in each group at the time of surgery are shown in Table 1.

Autoregulatory curves for each group are shown in Figure 1. The pressure ranges (mm Hg) for autoregulation of CBF (defined as the interval over which percent of control CBF did not deviate significantly from 100%) in the untreated groups are as follows: WKY-U 70–160, SHR-U 100–210, RHR-U 100–220. The ranges for WKY and SHR agree closely with previous measurements in an identical preparation. Also, the autoregulatory range for RHR-U is quite similar to that of SHR-U, indicating that these two forms of hypertension result in similar shifts of both lower and upper limits of the autoregulatory range.

Treatment largely prevented these shifts in the autoregulatory range (Figure 1, right panel). Autoregulatory ranges (mm Hg) in treated animals were as follows: WKY-T 60–160, SHR-T 80–170, and RHR-T 70–160. The upward shift in the autoregulatory range associated with hypertension was thus largely prevented by treatment in both models of hypertension, sug-

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Figure 1. Percent of control cerebral blood flow as a function of mean arterial blood pressure in untreated (left panel) and treated (right panel) experimental groups. Each point is the mean within a 10 mm Hg range of mean arterial pressure, e.g., the point at 100 represents the 100–109 mm Hg pressure interval. Total number of 1A arterioles studied: untreated 83; treated, 96.
Suggesting that there may be common microvascular adaptations operating in the cerebral vasculature of both models.

Figures 2 and 3 depict the changes in resting inner diameter in both the largest arterioles (1A, Figure 2) and smallest arterioles (4A, Figure 3). Data for WKY were pooled, because there were no statistical differences seen between treated and untreated normotensive rats. Both of the untreated hypertensives, SHR-U and RHR-U, exhibited reductions in arteriolar diameter of a magnitude consistent with previous studies in untreated SHR. Treatment prevented these reductions in IA diameter in both RHR and SHR (Figure 2), evidenced by resting diameter not significantly different from WKY. In the 4A, or smallest, arterioles, treatment in RHR did not prevent the reduction in resting diameter, while treatment in SHR resulted in a 4A diameter not significantly different from control (Figure 3). There appears to be some persistent constriction of the 4A in RHR-T that may be due to microvascular hypertrophy and/or a circulating vasoactive agent.

The extent to which microvascular hypertrophy was present and the degree of prevention by antihypertensive therapy is shown in Figures 4 and 5. Profound hypertrophy was evident in both the 1A and 4A of untreated SHR and RHR, consistent with previous observations. Following treatment, however, there was a persistent elevation in wall area in the 1A of treated SHR (Figure 4). Though this represents hypertrophy slightly less severe than in the untreated animal, it is nonetheless elevated compared to WKY. In addition, the treated RHR exhibited a 1A wall area significantly decreased from the untreated RHR, to a level not different from control. Thus, it appears that there may be a mechanism of hypertrophy operating in the SHR in addition to that accounted for by elevations in blood pressure; these pressure elevations are apparently the primary cause of hypertrophy in the untreated RHR. In the smallest arterioles (4A, Figure 5), the increase in wall mass is prevented in both SHR-T and RHR-T, indicating that the persistent hypertrophic mechanism in the SHR is operative only in the largest arterioles in the age group studied.

Table 2 shows the diameters of 1A and 4A arterioles during the resting, active state, and also during the
passive state induced by topical application of adenosine. Untreated SHR and RHR microvessels still exhibit marked capacity for dilation, and this dilation was significantly greater for 1A and 4A in the untreated than treated SHR. These data indicate that a large portion of the resting constriction seen in untreated hypertensive animals may have an active component. The fact that passive diameters are slightly, though not significantly, reduced in untreated hypertensive animals suggests that structural hypertrophy may also be making a contribution to resting constriction. Indeed, the increment in wall mass may confer a mechanical advantage for the development of active constriction.

As might be expected, microvascular pressures were elevated in the 1A and 4A of untreated SHR and RHR (Figures 6 and 7). Treatment prevented these elevations, and resulted in 1A and 4A intravascular pressures that were both significantly reduced from untreated levels, and no different from normotensive values. Consistent with previous studies in hypertensive rats, a proportionately larger fraction of the mean arterial pressure was transmitted to the microcirculation in untreated SHR (56.2%) and RHR (58.4%) compared to WKY (48.2%). Treatment, however, reduces these fractions to 51.2% in SHR−T and 49.5% in RHR−T. In effect, the large arteries preceding the microcirculation in WKY dissipated a larger fraction of the mean arterial pressure than in either the untreated SHR or RHR, but this difference was not so marked in treated SHR and RHR.

**Discussion**

The primary finding of the present study is that antihypertensive treatment initiated prior to the onset of hypertension in two mechanistically separate forms of the disease is effective in preventing structural and functional abnormalities associated with established hypertension. Further, it appears that the SHR, a model of essential hypertension, and RHR, a model of induced renal hypertension, respond to gradual elevations in mean arterial pressure with similar cerebrovascular adaptations. Finally, the existence of persistent microvascular abnormalities in both models following treatment suggests some subtle differences in the development of microangiopathy in two separate models of hypertension.

**Table 2.** Active and Passive Microvascular Diameters (μm) in Treated and Untreated WKY, SHR, and RHR

<table>
<thead>
<tr>
<th>Arteriolar</th>
<th>WKY−U</th>
<th>WKY−T</th>
<th>SHR−U</th>
<th>SHR−T</th>
<th>RHR−U</th>
<th>RHR−T</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A, active</td>
<td>54 ± 5</td>
<td>53 ± 6</td>
<td>43 ± 4</td>
<td>52 ± 4</td>
<td>42 ± 3</td>
<td>51 ± 5</td>
</tr>
<tr>
<td>1A, passive</td>
<td>88 ± 7</td>
<td>89 ± 8</td>
<td>77 ± 5</td>
<td>84 ± 7</td>
<td>74 ± 4</td>
<td>85 ± 7</td>
</tr>
<tr>
<td>% increase</td>
<td>63 ± 4</td>
<td>68 ± 5</td>
<td>77 ± 8</td>
<td>62 ± 6*</td>
<td>73 ± 6</td>
<td>67 ± 5</td>
</tr>
<tr>
<td>4A, active</td>
<td>15 ± 1</td>
<td>14 ± 2</td>
<td>10 ± 1</td>
<td>14 ± 1</td>
<td>12 ± 2</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>4A, passive</td>
<td>22 ± 3</td>
<td>24 ± 1</td>
<td>18 ± 1</td>
<td>23 ± 1*</td>
<td>20 ± 2</td>
<td>19 ± 1</td>
</tr>
<tr>
<td>% increase</td>
<td>55 ± 6</td>
<td>64 ± 2</td>
<td>75 ± 4</td>
<td>63 ± 3*</td>
<td>70 ± 7</td>
<td>64 ± 4</td>
</tr>
</tbody>
</table>

All values are mean ± SEM.

*p < 0.05 vs. untreated animal; unpaired t test.
abnormalities associated with the disease. As implied in a previous study, the reversal of structural adaptations is responsible for the restoration of normal CBF autoregulation, but the present study is among the first to combine an analysis of both CBF autoregulation and changes in cerebral microvascular dimensions. Indeed, the results of the present study and a previous preliminary investigation suggest that the regression or prevention of microvascular changes are responsible for the restoration of flow autoregulation to normotensive levels.

The prevention of vascular hypertrophy was a very definite finding in the arterioles of treated SHR and treated RHR in the present study, though the SHR manifested a degree of hypertrophy in large arterioles in spite of treatment. The factors accounting for the predominant absence of hypertrophy in the hypertensive rats are unclear. Recent studies in large vessels of rats have established that increases in vessel wall mass are due primarily to pressure-induced smooth muscle cell hypertrophy, not hyperplasia. By contrast, Lee et al. have determined that smooth muscle cell hyperplasia, not hypertrophy, is primarily responsible for medial hypertrophy in mesenteric arterioles of SHR, while studies suggest that this medial hypertrophy offers a mechanical advantage for generation of active tension in the arterioles of SHR. Assuming that similar circumstances apply to the cerebral microcirculation, it would be of interest to investigate the reasons for regression or prevention of this increased wall mass, regardless of whether it is due to hyperplasia or hypertrophy. One possibility is that the antihypertensive drugs used had a direct effect on the cerebral microvessels other than that expected with reduction of mean arterial pressure. Hydralazine, while a potent vasodilator, would be expected to have a marked effect on CBF autoregulation. However, because this drug is administered orally and cleared quite rapidly, residual effects should be minimal. Also, increments in CBF are not apparent following extended treatment of SHR with hydralazine, so a sustained vasoactive effect is probably not present. Chlorothiazide, a diuretic, may affect the accumulation of sodium and water in the walls of resistance vessels, thereby having a direct effect on the vessel independent of the reduction in blood pressure. Reserpine, by virtue of its blocking sympathetic outflow, would be expected to eliminate any direct role of the sympathetic nervous system.
system in mediating the development of hypertrophy, independent of elevations in blood pressure. However, the degree to which reserpine inhibits sympathetic outflow to the cerebral microvessels and the actual significance of this innervation are unclear. Since findings are similar for several different antihypertensive regimes, it is unlikely that these drugs have appreciable direct effects on the cerebral circulation. Rather, the reversal of peripheral structural and hemodynamic changes is generally accepted to be due to the reduction in blood pressure since similar regression of vascular pathology is seen following removal of renal artery clips in experimental renal hypertension.

A high degree of correlation between increments in blood pressure and vascular smooth muscle cell numbers in untreated hypertensive rats exists, suggesting a role for increased wall stress or blood pressure in mediation of hypertrophic cellular growth. Increments in blood pressure, especially at the microvascular level, will result in a transient increase in wall stress, assuming that reductions in vascular diameter or increases in wall thickness are not present. Indeed, a previous study demonstrated that, while microvascular pressures are elevated in SHR, microvascular wall stress is essentially normal in most arterioles. Thus, it appears that a combination of microvascular hypertrophy and resting constriction represents a dynamic process by which the microvasculature can adapt to hypertension. The existence of hypertrophy may in fact potentiate the ability of the microvessels to maintain an active constriction. However, if the increment in blood pressure is reduced or prevented, there should necessarily be a reduction in wall thickness/area, i.e., a regression of hypertrophy, to restore resting microvascular wall stress to normal levels. The prevention of hypertension in the present study was effective in largely preventing microvascular hypertrophy, presumably by eliminating a potential stimulus for hypertrophy—an increase in blood pressure leading to an increase in wall stress. The extent to which vascular hypertrophy and hyperplasia play a role in the increased vascular wall mass is unclear, though studies on large arteries suggest that control of these growth processes may be mediated by different factors. Further, the approach in the present study, i.e., the prevention of hypertension, would eliminate those factors complicating the assessment of vascular hypertrophy following treatment of long-standing hypertension: accumulation of elastin and collagen, accumulation of endothelial fibrinohyalin, and, loss of vascular elasticity. These structural alterations would not be expected to be readily reversed by any duration of treatment, and would account for varying degrees of success in restoring CBF autoregulation following long-standing hypertension.

The apparent differences between SHR and RHR, both treated and untreated, in terms of adaptations to hypertension and responses to treatment, deserve comment. Both SHR and RHR exhibit quite similar microvascular changes, as evidenced by significant resting constriction, wall hypertrophy, and elevated microvascular pressure. The structural adaptations to established hypertension therefore account for both the upward shift of the CBF autoregulatory range, and proportionate shift of total cerebrovascular resistance to the microcirculation (present study; Harper and Bohlen), since total CBF is not different between normotensive and untreated hypertensive rats. Both SHR and RHR exhibit interesting microvascular responses following treatment as well. If treatment is initiated prior to the development of frank hypertension in both models, one would expect that any deviations from normal values would be due to a fundamental variation in pathogenesis, all other things being equal. In the treated SHR, a remarkable finding was the evidence of microvascular hypertrophy in the largest arterioles. Because increments in blood pressure were not present as mediators of hypertrophy, other factors must account for this change. While the sympathetic nervous system has been implicated in providing a "trophic" influence on the growth of smooth muscle cells in hypertension, it is unlikely that this mechanism could mediate an increase in wall mass in the present study if reserpine is used in the treatment regimen. However, it is unclear to what extent reserpine was effective in reducing sympathetic outflow to the cerebral microvessels. It is possible, however, that there might be a preprogrammed hyperplastic response to the microvascular smooth muscle cells, similar to that found in the aorta under comparable conditions of treatment in a previous study.

Regardless of its cause, this evidence of microvascular hypertrophy may indicate a generalized predisposition to hypertrophy in SHR, as suggested by longitudinal studies in the hind limb of SHR, and by denervation studies in the cerebral microvasculature of stroke-prone SHR.

In the treated RHR, microvascular parameters were essentially normal, except for evidence of resting constriction in the smallest arterioles. Given that hypertrophy was not present in these vessels in treated RHR, it must be assumed that a direct constrictor influence exists. One possibility is the existence of a circulating vasoconstrictor peculiar to the form of hypertension: angiotensin II certainly emerges as a possibility. The fact that only the smallest arterioles constric suggests a differential dose-response sensitivity to the vasoactive substance in question. This may also represent the initial stage of a process of ascending microvascular constriction demonstrated during the development of hypertension in the cremaster muscle of renal hypertensive rats. An alternate possibility is that the slight elevation in microvascular pressure delivered to the 4A (40.1 ± 2.6 mm Hg in the 3A of RHR-T vs. 35.3 ± 4.0 mm Hg in the 3A of WKY) may induce a mild myogenic constriction, since this control mechanism was recently shown to be of significant consequence in cerebrovascular flow regulation. While the reason for this persistent arteriolar constriction is unclear, its presence implies that treatment initiated prior to the development of hypertension may not completely eliminate the pathologic processes involved. Whether or not this process continues during periods of
extended treatment would be the subject of extensive longitudinal studies.

In summary, the primary application of the present study is that a reduction in blood pressure at the time of onset of hypertension, or prevention of blood pressure increments altogether, can be of significant value in improving the autoregulation of CBF by reducing or eliminating the prospect of structural alterations in cerebral microvessels. While structural adaptations have long been assumed to account for variations of CBF autoregulation with and without treatment of hypertension, the present study demonstrates this to be the case by including both structural and functional analyses of CBF autoregulation. There appear to be minor microvascular abnormalities that persist in spite of treatment in both hypertensive models; these are assumed to be due to variations in the pathogenesis of each form of the disease. It is clear, however, that early treatment largely prevents vascular damage in hypertension and may reduce predisposition to vascular atherosclerosis. This would reduce vascular complications, e.g., thrombosis leading to stroke, in addition to those that might be associated with acute elevations in blood pressure.

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