Chronic Antihypertensive Treatment in the Rat Reverses Hypertension-Induced Changes in Cerebral Blood Flow Autoregulation

SISSEL VORSTRUP, DAVID I. BARRY, JENS OLE JARDEN, ULRIK GERNER SVENSDEN, OTTO BRAENDSTRUP, DAVID I. GRAHAM, AND SVEND STRANDGAARD

SUMMARY Cerebral blood flow (CBF) autoregulation was studied in renal hypertensive rats receiving chronic antihypertensive treatment. Young Wistar Kyoto rats (WKY) were made hypertensive by the Loomis procedure i.e. partial infarction of one kidney with contralateral nephrectomy. Systolic tail blood pressure was measured at 2-week intervals throughout the study. After two months, by which time the rats had been severely hypertensive for 5-6 weeks, antihypertensive treatment was begun; reserpine, dihydralazine and hydrochlorothiazide were administered in the drinking water. Blood pressure fell rapidly to normotensive levels and remained so. Following two months of antihypertensive treatment, the lower blood pressure limit of CBF autoregulation was studied during controlled bleeding. In age-matched untreated renal hypertensive WKY, the lower limit of autoregulation was in the mean arterial pressure range 90–109 mm Hg, as compared to 50–69 mm Hg in age-matched normotensive WKY. In contradistinction to the untreated rats, the treated rats had a normal lower limit of autoregulation, i.e. 50–69 mm Hg. It was inferred that the reversal of the functional change in CBF autoregulation reflected reversal of hypertension-induced cerebrovascular hypertrophy/hyperplasia.

IN CHRONIC HYPERTENSION, resistance vessel walls thicken in order to increase vascular resistance and protect against high intraluminal pressure. One consequence of these adaptive changes is resetting of the blood pressure range over which cerebral blood flow (CBF) can be maintained constant by autoregulation. The lower blood pressure limit of CBF autoregulation is the pressure at which autoregulatory dilatation becomes inadequate and flow decreases with pressure. In hypertension, the lower limit of CBF autoregulation is shifted towards high pressure, presumably as autoregulatory vasodilatation is impaired by resistance vessel wall thickening and luminal narrowing. This hypertension-induced shift in the lower limit of CBF autoregulation has been shown in man, 1,2 in the baboon3 and in the rat. 4 Hypertension-induced adaptation has also been shown for the upper limit of CBF autoregulation in the baboon. 3 Hence it is widely accepted that CBF, hypertensive vascular changes impair the tolerance to acute hypotension, but improve the tolerance to acute rises in blood pressure.

The clinical consequence of the shift in the limits of CBF autoregulation is that if the blood pressure of a hypertensive patient is rapidly lowered to normotensive levels, CBF will fall, possibly causing ischaemic brain damage. Thus rapid and severe pharmacological reduction of blood pressure as in emergency treatment of hypertension has been criticised. 6,7 With chronic treatment of hypertension and a gradual normalisation of blood pressure there is time for reversal of some of the structural and haemodynamic consequences of hypertension. This may apply to CBF autoregulation in man and old spontaneously hypertensive rats, the latter being better able to maintain CBF during an acute blood pressure drop than are untreated rats. 8 The present study examined whether chronic antihypertensive treatment of renal hypertensive rats would reverse the autoregulatory shift known to be present after 2 months of hypertension and restore a normal lower limit of autoregulation to the cerebral circulation.

Material and Methods

The experiments were performed on male Wistar Kyoto rats (WKY, F24) supplied by Mollegaard Ltd., Denmark. All rats were housed in the same room, and had free access to food and water. No salt or corticosteroids were given.

Induction of Hypertension and Treatment

At the age of one month, 60 rats were made chronically hypertensive by a modification of the Loomis technique. 9 During halothane anaesthesia the right kidney was removed and one branch of the left renal artery was ligated, immediately resulting in ischaemia of approximately 50–70% of the kidney surface. The kidney was then placed subcutaneously, where it would become encapsulated by fibrous tissue. An age matched unoperated group of 15 WKY served as a control group. Systolic blood pressure (SAP) was measured at 2-week intervals by the tail-cuff photoelectric pulse pick-up method. In about 60% of the rats, tail pressure rose to between 200 and 240 mm Hg within 3–4 weeks, as compared to 130 mm Hg in the unoperated control WKY. The remaining rats either died, remained normotensive or developed severe debilitating hypertension, and were thus discarded. After two months, 30 of the renal hypertensive rats (RHR) were chosen for further study. These were sturdy, growing normally and without signs of neurological...
impairment. The development of hypertension in those rats subsequently used for the autoregulation study is shown in Fig. 1. It was known from our earlier work that 2 months after becoming hypertensive, RHR exhibit an adaptive shift in the lower limit of CBF autoregulation of 20–30 mm Hg. Thus antihypertensive treatment was started at this point.

Of the 30 RHR chosen for further study, 15 were placed on chronic antihypertensive treatment and 15 were untreated. The number of rats was in excess of the number of good autoregulation studies required (six) in order to allow for deaths, inadequate treatment and experimental failures. Treatment was administered in the drinking water in the form of reserpine 1.4 mg/l, dihydralazine 80 mg/l, and hydrochlorothiazide 100 mg/l. For the first 4 days the solution was diluted 50% in order that blood pressure should not fall too rapidly. Daily intake per rat averaged 44 ml. After 2 months of treatment, 6 of the rats were used for the CBF autoregulation study, together with 6 untreated RHR and 6 normotensive control WKY. Antihypertensive treatment was withdrawn 5–6 hr before the autoregulation study.

CBF Measurement

CBF was measured with the intraarterial $^{133}$Xenon technique modified for rat studies. Anaesthesia was induced with 4% halothane, and maintained with 0.8% halothane in 30% $O_2$:70% $N_2O$. The rats were tracheostomised, paralysed with suxamethonium (40 mg/kg, and artificially ventilated. Both femoral arteries were cannulated, one for recording blood pressure, the other for blood sampling. A femoral vein was also cannulated for blood or drug administration. All extracerebral branches of the right common carotid artery were ligated, and the scalp and muscle overlying the right side of the calvarium was removed in order to minimize the extracerebral distribution of injected $^{133}$Xenon. The animals were heparinised (5000 IU/kg), and a polyethylene catheter (PP25) introduced retrogradely into the external carotid stump, with the tip positioned at the carotid bifurcation. The common carotid artery was not clamped during the cannulation. Surgery lasted for approximately 45 minutes, after which the animal was left to stabilize for one hour.

For each determination of CBF a 10–15 μl saline bolus containing $^{133}$Xenon (5–10 mCi/ml, Amersham) was injected into the carotid catheter. Clearance of $^{133}$Xenon from the brain was followed by external detection with a heavily collimated NaI(Th) crystal placed over the head, ipsilateral to the injection side. CBF was calculated by the initial slope method using the formula:

$$ CBF = -\lambda \times \ln 10 \times D_s \times 100 \text{ (ml/100g·min)} $$

where the blood-brain partition coefficient for grey matter, $\lambda$, is 0.87 ml/g, and $D_s$ is the initial slope (the first 10–15 s) of a semilogarithmic recording of the clearance curve. The peak value of around 2000 cps ensured that the linearity of the clearance curve was not affected by low counting statistics. A correction curve was used to correct for the activity remaining from previous measurements when that activity exceeded 2% of the peak activity. Such correction was rarely necessary however.

Arterial tension of carbon dioxide (PaCO$_2$) and oxygen (PaO$_2$) together with pH (pHa), were measured at intervals during surgery/stabilization, and at each CBF measurement, with conventional microelectrodes (Radiometer, Copenhagen). The blood withdrawn for these measurements were substituted with blood from donor rats of the same condition (i.e. treated RHR, untreated RHR or normotensive). The rats were maintained at normocapnia (PaCO$_2$, 39–41 mm Hg) by adjustment of ventilation volume. Body temperature was maintained close to 37°C by means of a rectal-thermistor-controlled heating table. Arterial blood pressure was recorded throughout the study, with mean arterial pressure (MAP) and heart rate (HR) being calculated from the recording.

Autoregulation Study

The lower limit of CBF autoregulation was determined by controlled stepwise haemorrhagic hypotension in the 3 groups of rats. Following the one hour stabilization period, 2–3 baseline measurements were performed at 10 minutes intervals. To permit CBF measurements along the autoregulatory plateau in the normotensive control group and the treated RHR, blood pressure was raised in approximately 10 mm Hg increments by a slow intravenous infusion of angiotensin II amine (Hypertensin, CIBA), 5–20 μg/min. Blood pressure was then reduced stepwise by controlled withdrawal of sufficient blood to lower MAP by 10 mm Hg. At each level, MAP was allowed to stabilize for 10 minutes before CBF was measured. In this way, an autoregulation curve based on 8–12 measurements was delineated for each rat. The study typically lasted 3 hours.

Neuropathology

Following the CBF study, a neuropathological examination was undertaken. The rats were maintained in a stable condition for another two hours after the lowest blood pressure had been reached, that is 30–40 mm Hg. They were then sacrificed by perfusion fixation with FAM (40% formaldehyde:glacial acetic acid:ethanol, 1:1:8 by volume). The brains were left in situ for 24 hours, then removed and immersed in FAM for another 48 hours before being processed for light microscopy. Each brain was cut in a similar way into eight coronal slices (five forebrain and three hindbrain) and embedded in paraffin. Particular care was taken to identify the left and right hemispheres. Seven-to eight-micrometer sections were stained using a technique combining Luxol fast blue and cresyl violet, and also with hematoxylin-eosin. All brains were coded in a random number such that the neuropathological examination was performed blind, with the code being broken only after completion of this and related studies.
Statistics

Data for each series are given as the mean ± 1 SD after grouping according to MAP, using intervals of 20 mm Hg. Comparisons within the series were made by one way analysis of variance together with the Dunnett multiple comparison test16 using the MAP range in which baseline MAP fell as control range. The lower limit of CBF autoregulation in the present study is defined as the MAP range at which CBF (% baseline) fell significantly below the autoregulatory plateau of around 100% baseline CBF. Inter-series statistical comparisons were not made. Results were accepted as significant at p < 0.05.

Results

Blood Pressure

The awake SAP was between 100 and 130 mm Hg in the control normotensive rats. After the Loomis procedure, hypertension ensued with SAP reaching 200–240 mm Hg within 4–5 weeks. In the untreated RHR, SAP remained at that level during the following 2–3 months. In those RHR that were given antihypertensive treatment, SAP fell to between 80 and 120 mm Hg over 4–5 days, remaining at that level throughout the treatment period. The individual SAP curves are shown in figure 1. At the time of the autoregulation study, SAP was 121 ± 10 mm Hg in control rats, 221 ± 15 in untreated RHR and 88 ± 10 in treated RHR (x ± 1 SD, n = 6). Under anaesthesia, the corresponding MAP was 70 ± 4, 133 ± 11 and 80 ± 7 mm Hg, respectively (table 1). Thus anaesthesia had a marked baro depressant effect in the control and untreated rats, but not in the treated RHR.

Body and Heart Weight

Body weight increased from around 80g to 380 ± 12g in the control rats, 348 ± 30g in untreated RHR and 364 ± 13g in treated RHR, indicating that all rats were growing fairly normally. Left ventricular mass at the end of the study was 0.29 ± 0.03% of body wt in control rats, 0.40 ± 0.04% in untreated RHR and 0.32 ± 0.03% in treated RHR, indicating reversal of the structural changes in cardiac muscle in the treated RHR.

Autoregulation Study

Baseline measurements of CBF, MAP and other relevant physiological parameters are shown in table 1. Control and untreated RHR were similar in all respects except for the significantly higher MAP in the untreated RHR. Treated RHR were similar to control for all parameters.

In table 2, all data measured during the autoregulation study are shown grouped according to MAP. Intervals of 20 mm Hg have been used except for the range 20–29 mm Hg. CBF has been calculated as percent of baseline CBF. The autoregulation curves for the three groups of rats are shown in figure 2. For statistical comparison, all results have been compared with the pressure range of the baseline MAP i.e. 70–89 mm Hg for controls and treated RHR, and 130–149 mm Hg for untreated RHR. The lower limit of autoregulation is defined in the present study as the MAP range at which CBF% baseline fell significantly below the autoregulatory plateau of around 100%. In control normotensive rats, values of CBF around 100% were maintained down to the MAP range 70–89 mm Hg, the lower limit of autoregulation being in the range 50–69 mm Hg. The untreated RHR were only able to autoregulate effectively to a MAP range of 110–129 mm Hg, the lower limit of autoregulation being 90–109 mm Hg. This indicates a 40 mm Hg shift in the lower limit of CBF autoregulation after 4 months of hypertension, as compared to a 20–30 mm Hg shift after 2–3 months of hypertension.4 In contradistinction to the untreated RHR, the treated RHR were able to autoregulate CBF down to the blood pressure range 70–89 mm Hg, and thus had a normal lower limit of CBF autoregulation of 50–69 mm Hg.

Neuropathology

As judged by uniform blanching and hardness of the specimen, satisfactory fixation was achieved in all animals, and cytological artefacts such as 'dark cell' and 'hydropic cell'15,17 were absent. The ischaemic lesions found in 4 of the rats, usually small foci involving microvacuolation of cells, incrustation and shrinkage of cytoplasm and nucleus, were of the type reported previously in FAM fixed rat brain.15,18,19 Such lesions were found in RHR after haemorrhagic or acute pharmacological blood pressure lowering.4,20,21

Lesions were found in 1 of 6 normotensive control WKY, 1 of 6 treated RHR and 2 of 6 untreated RHR. In the normotensive control WKY there were 10 small lesions in the right hemisphere. In both untreated RHR the lesions were bilateral; in one rat there were 4 small lesions, two of which were situated posteriorly in the arterial boundary zone between the distribution of the middle and anterior cerebral arteries: in the other rat there was extensive necrosis of the right hemisphere and two left-sided lesions. In the single treated RHR there were 5 small right-sided lesions. In an earlier
study, lesions were found in 4 of 8 untreated RHR after haemorrhagic hypotension. The ischaemic lesions probably result from the combined effect of the hypertensive insult and carotid cannulation. The study indicates that the treated RHR were less susceptible to ischaemia during severe haemorrhagic hypotension that the untreated RHR, reflecting the restoration of a normal lower limit of CBF autoregulation after antihypertensive treatment.

Morphometric measurements of the type undertaken by Nordberg and Johansson were not undertaken in this study. However, by light microscopy of the paraffin sections it was our subjective impression that the walls of the larger cerebral arteries (upper end of the internal carotid and stems of the anterior and middle cerebral arteries) in the untreated group of hypertensive rats were thinned compared with the control and treated groups of animals. Definite evidence of hypertensive cerebral vascular disease was seen in one of the untreated hypertensive animals in which there was fibrinoid necrosis of a single pial artery.

**Discussion**

The main finding was that chronic treatment of renal hypertension in the rat restored a normal lower limit of autoregulation to the cerebral circulation. That only minor ischaemic lesions were induced by haemorrhage in a single treated rat is a reflection of their normal autoregulation. It is generally assumed that the functional shift in CBF autoregulation induced by hyper-

## Table 1

<table>
<thead>
<tr>
<th>MAP (mm Hg)</th>
<th>CBF (ml/100 g·min)</th>
<th>CBF (% of baseline)</th>
<th>HR (b/min)</th>
<th>PaCO₂ (mm Hg)</th>
<th>pHₐ</th>
<th>PaO₂ (mm Hg)</th>
<th>T (°C)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control WKY</td>
<td>130-149</td>
<td>78 ± 14</td>
<td>103 ± 5</td>
<td>141 ± 9</td>
<td>240 ± 17</td>
<td>40.5 ± 1.8</td>
<td>7.39 ± 0.06</td>
<td>123 ± 20</td>
</tr>
<tr>
<td>Untreated RHR</td>
<td>110-129</td>
<td>76 ± 9</td>
<td>99 ± 19</td>
<td>118 ± 8</td>
<td>243 ± 16</td>
<td>42.1 ± 2.9</td>
<td>7.42 ± 0.03</td>
<td>142 ± 12</td>
</tr>
<tr>
<td>Treated RHR</td>
<td>90-109</td>
<td>75 ± 12</td>
<td>97 ± 7</td>
<td>101 ± 7</td>
<td>235 ± 10</td>
<td>38.9 ± 2.4</td>
<td>7.46 ± 0.02</td>
<td>155 ± 20</td>
</tr>
<tr>
<td>70-89</td>
<td>73 ± 12</td>
<td>99 ± 5</td>
<td>77 ± 7</td>
<td>231 ± 16</td>
<td>39.7 ± 2.4</td>
<td>7.44 ± 0.05</td>
<td>136 ± 29</td>
<td>37.2 ± 0.5</td>
</tr>
<tr>
<td>50-69</td>
<td>62 ± 17*</td>
<td>84 ± 16*</td>
<td>62 ± 5</td>
<td>233 ± 27</td>
<td>38.5 ± 1.7</td>
<td>7.45 ± 0.03</td>
<td>145 ± 22</td>
<td>37.3 ± 0.5</td>
</tr>
<tr>
<td>30-49</td>
<td>50 ± 13*</td>
<td>70 ± 19*</td>
<td>40 ± 6</td>
<td>245 ± 37</td>
<td>37.2 ± 3.2</td>
<td>7.42 ± 0.15</td>
<td>137 ± 14</td>
<td>37.4 ± 0.6</td>
</tr>
<tr>
<td>20-29</td>
<td>31 ± 7*</td>
<td>43 ± 8*</td>
<td>24 ± 4</td>
<td>263 ± 71</td>
<td>30.7 ± 8.3*</td>
<td>7.37 ± 0.06</td>
<td>151 ± 32</td>
<td>36.7 ± 0.4</td>
</tr>
</tbody>
</table>

Values are mean ± 1 SD. *Untreated RHR vs control WKY, p < 0.01. †Treated RHR vs untreated RHR, p < 0.01.

---

## Table 2

<table>
<thead>
<tr>
<th>MAP (mm Hg)</th>
<th>CBF (ml/100 g·min)</th>
<th>CBF (% of baseline)</th>
<th>HR (b/min)</th>
<th>PaCO₂ (mm Hg)</th>
<th>pHₐ</th>
<th>PaO₂ (mm Hg)</th>
<th>T (°C)</th>
<th>No. of measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control WKY</td>
<td>130-149</td>
<td>78 ± 14</td>
<td>103 ± 5</td>
<td>141 ± 9</td>
<td>240 ± 17</td>
<td>40.5 ± 1.8</td>
<td>7.39 ± 0.06</td>
<td>123 ± 20</td>
</tr>
<tr>
<td>Untreated RHR</td>
<td>110-129</td>
<td>76 ± 9</td>
<td>99 ± 19</td>
<td>118 ± 8</td>
<td>243 ± 16</td>
<td>42.1 ± 2.9</td>
<td>7.42 ± 0.03</td>
<td>142 ± 12</td>
</tr>
<tr>
<td>Treated RHR</td>
<td>90-109</td>
<td>75 ± 12</td>
<td>97 ± 7</td>
<td>101 ± 7</td>
<td>235 ± 10</td>
<td>38.9 ± 2.4</td>
<td>7.46 ± 0.02</td>
<td>155 ± 20</td>
</tr>
<tr>
<td>70-89</td>
<td>73 ± 12</td>
<td>99 ± 5</td>
<td>77 ± 7</td>
<td>231 ± 16</td>
<td>39.7 ± 2.4</td>
<td>7.44 ± 0.05</td>
<td>136 ± 29</td>
<td>37.2 ± 0.5</td>
</tr>
<tr>
<td>50-69</td>
<td>62 ± 17*</td>
<td>84 ± 16*</td>
<td>62 ± 5</td>
<td>233 ± 27</td>
<td>38.5 ± 1.7</td>
<td>7.45 ± 0.03</td>
<td>145 ± 22</td>
<td>37.3 ± 0.5</td>
</tr>
<tr>
<td>30-49</td>
<td>50 ± 13*</td>
<td>70 ± 19*</td>
<td>40 ± 6</td>
<td>245 ± 37</td>
<td>37.2 ± 3.2</td>
<td>7.42 ± 0.15</td>
<td>137 ± 14</td>
<td>37.4 ± 0.6</td>
</tr>
<tr>
<td>20-29</td>
<td>31 ± 7*</td>
<td>43 ± 8*</td>
<td>24 ± 4</td>
<td>263 ± 71</td>
<td>30.7 ± 8.3*</td>
<td>7.37 ± 0.06</td>
<td>151 ± 32</td>
<td>36.7 ± 0.4</td>
</tr>
</tbody>
</table>

Values are mean ± 1 SD. Each range vs baseline MAP range i.e. Control WKY and Treated RHR 70-89 mm Hg; Untreated RHR 130-149 mm Hg. *p < 0.01; †p < 0.05.
by guest on April 9, 2017 http://stroke.ahajournals.org/ Downloaded from

Lower Limit of Autoregulation

The lower limit of CBF autoregulation is the blood pressure at which autoregulatory vasodilatation of cerebral blood vessels becomes inadequate to maintain CBF, which then falls. This should not be equated with maximum dilatation of cerebral vessels as it has been shown that pial vessels will continue to dilate as blood pressure is brought below the lower limit of autoregulation i.e. whilst CBF is falling. As CBF is the same in the untreated RHR as in the treated and control rats, despite a higher arterial pres-

regulation to a slightly higher blood pressure, although the effect is minor compared with that in other organs such as the kidney. Pharmacological ganglion blockade will prevent this effect and thus a 'true' lower limit of autoregulation may be that obtained during ganglion blockade. In the present rat studies, the animals were anaesthetised with 0.8% halothane and paralysed with suxamethonium, both of which have slight ganglion blocking properties. In a similar study, the lower limit of CBF autoregulation in SHR and WKY during haemorrhagic hypotension was not influenced by the ganglion blocker trimetaphan (166 μg/kg/min) (Barry et al, unpublished observation). Furthermore, chemical sympathectomy (intraventricular 6-hydroxy dopamine) does not influence the lower limit of autoregulation during haemorrhagic hypotension in SHR. Thus under the experimental conditions used the lower limit of autoregulation is not influenced by sympathetic activity and the hypertensive shift in the lower limit reflects mainly structural changes in the cerebral vessels. For this reason we consider the choice of a lower limit of autoregulation during controlled bleeding as suitable for the present study of the effect of chronic antihypertensive treatment.

The results in the treated RHR must be interpreted with due regard to possible direct effects of the drugs used. Thus whether reserpine, dihydralazine and hydrochlorothiazide could have had an influence on CBF autoregulation by means other than their combined antihypertensive action deserves comment. Acute blood pressure lowering by certain drugs (e.g. the direct vasodilator dihydralazine) may bring pressure below the lower limit of autoregulation in RHR without any fall in CBF. This dilatation of cerebral vessels appears to 'extend' the lower limit of autoregulation. As drug treatment was withdrawn from the RHR 5–6 hr prior to the autoregulation study, and as dihydralazine is fairly rapidly metabolized, little residual effect would be expected. Reserpine, which accumulates in the body, could prevent a sympathetic shift during haemorrhagic hypotension but as discussed above, there is probably little such influence on CBF autoregulation under the present experimental conditions. The diuretic hydrochlorothiazide might influence resistance vessel water-logging and thus augment the reversal process. These direct effects could supplement the effects of CBF autoregulation of the reversal of structural changes that probably resulted from lowering of blood pressure. However, they would not be expected to account for the normal lower limit of CBF autoregulation in the treated RHR. Furthermore, it is generally accepted that the reversal of peripheral structural and haemodynamic changes is due to blood pressure lowering rather than any direct effect of the drugs used: hence findings are similar with a number of antihypertensive regimes and, in the case of hypertension induced by renal artery clipping, clip removal.

Resistance Vessel Adaptation in Hypertension

As CBF is the same in the untreated RHR as in the treated and control rats, despite a higher arterial pres-

Figure 2. Lower part of the cerebral blood flow autoregulation curve in renal hypertensive rats after 8 weeks of antihypertensive treatment with reserpine, dihydralazine and hydrochlorothiazide. Also shown are the corresponding curves for untreated renal hypertensive rats and normotensive controls. CBF measurements were made at approximately 10-mm Hg MAP intervals during angiotensin II induced elevation of MAP and during controlled haemorrhagic hypotension. The results are expressed as percent baseline CBF and grouped at 20 mm Hg MAP intervals. The lower limit of autoregulation was in the MAP range 50–69 mm Hg in control normotensive rats; in the untreated renal hypertensive rats the lower limit was shifted to the MAP range 90–109 mm Hg whereas in the treated rats it was restored to normal i.e. 50–69 mm Hg. Values are mean ± SEM.
sure, cerebrovascular resistance must be higher in the former. The mechanism behind the increased resistance in hypertension is probably structural adaptive changes in cerebral resistance vessels i.e. arterioles, as is the case elsewhere in the body. Medial thickening with encroachment of cerebral arterial and arteriolar lumen has been demonstrated morphometrically in man and rat. The morphological changes are better described for peripheral vessels than cerebral vessels. In the early phase of hypertension, these changes consist of smooth muscle cell hypertrophy and medial hyperplasia, largely proportional to the pressure level, together with an increased logging of water and electrolytes in the vessel wall. In longstanding hypertensive disease, additional changes include accumulation of fibrous proteins, elastin and collagen, and degeneration of the muscle cells. The reversibility of the functional adaptive changes would be expected to depend on the nature of the underlying structural changes: the initial changes of smooth muscle cell hypertrophy and water-logging probably are reversible following normalisation of blood pressure, whereas this is less likely with the degenerative changes and connective tissue proliferation.

Development or complete regression of the structural adaptation can occur in a matter of weeks. The former depends mainly on the degree of hypertension whereas the latter depends on addition on the duration of hypertension and age of the animal. Adaptive changes in the cerebral circulation have been demonstrated after 2 months of hypertension in baboon and rat. The reversibility of cerebrovascular adaptive changes after normalisation of blood pressure has not previously been shown. However in some effectively treated hypertensive patients, there was a tendency for the lower limit of autoregulation to be nearer to normal than in untreated or less effectively treated patients. Furthermore, in aged (2 year old) SHR, antihypertensive treatment appeared to improve the tolerance of CBF to haemorrhagic hypotension, indicating that autoregulation may have been improved. As the lower limit of autoregulation in the treated and untreated rats was not determined in that study, it is not possible to assess the degree to which the hypertension-induced changes may have been modified by treatment. However, as the animals had long-established hypertension, and as treatment seems not to reduce medial thickening of cerebral arteries in aged SHR (1 year old), only a partial reversal of the shift in CBF autoregulation would be expected. The present finding that after 2 months of treatment, the lower limit of CBF autoregulation was normal would fit with the time course of regression in other vascular beds. Thus in young SHR, drug treatment reversed the adaptive changes in the heart and peripheral resistance vessels in 3–5 weeks. Similar observations were made in young renal hypertensive rats after removal of a renal artery clip.

In the present study, antihypertensive treatment was started 2 months after induction of hypertension, by which time the rats had been severely hypertensive for about 6 weeks. In an earlier study of RHR and SHR, we have shown that the lower limit of CBF autoregulation is shifted 20–30 mm Hg to the right on the blood pressure axis after a similar period of hypertension. Thus the RHR in the present study would be expected to have undergone adaptation of the cerebral circulation by the time that treatment was started. Antihypertensive treatment effectively maintained blood pressure at low-normal levels and reversed the hypertensive adaptive change in the lower limit of CBF autoregulation. In the untreated RHR, the lower limit of autoregulation was shifted 30–40 mm Hg towards higher pressure after 4 months as compared to 20–30 mm Hg after 2–3 months in the earlier study, indicating that the structural vascular changes were not complete at the time of starting treatment, and that the treatment prevented further development of vascular changes. Whether more longstanding hypertensive adaptation of the cerebral circulation could be reversed by antihypertensive treatment is unknown, although partial reversal is indicated by the study in SHR mentioned above. Similarly, peripheral vascular changes could only be partially reversed by antihypertensive treatment of elderly animals with long-standing hypertension.

Although no precise time factor can be derived, it can be inferred from the above-mentioned observations and the findings of the present study that reversal of the hypertension-induced adaptive changes will take place during the first few weeks or months after lowering of blood pressure towards normal levels. Thereafter, only moderate changes with only minor influence on the haemodynamic parameters will occur. However, longstanding antihypertensive treatment may prevent or postpone the development of further degenerative adaptive changes. These findings are relevant to clinical antihypertensive treatment of young and middle-aged patients, in whom a gradual but complete normalisation of blood pressure may lead to a normal autoregulation of cerebral blood flow.

Acknowledgment

This study was supported by the Danish Heart Foundation and the Danish Medical Research Council. We are extremely grateful to Anne Mette Elle and Anne-Iise Aanonsen for excellent technical and secretarial assistance.

Reference

Lancet 2: 510, 1979


Chronic antihypertensive treatment in the rat reverses hypertension-induced changes in cerebral blood flow autoregulation.
S Vorstrup, D I Barry, J O Jarden, U G Svendsen, O Braendstrup, D I Graham and S Strandgaard

*Stroke.* 1984;15:312-318
doi: 10.1161/01.STR.15.2.312

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/15/2/312

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/