Decreased Local Cerebral Blood Flow in Young and Aged Spontaneously Hypertensive Rats

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Abstract. Local cerebral blood flow (LCBF) was measured using the \( ^{14} \)C iodoantipyrine method in 56 discrete brain regions in spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto rats (WKY) of 4 months old (young-adult) and 16–17 months old (aged). Compared with the young-adult WKY, in both the young-adult and aged SHR, LCBF was reduced in scattered brain regions, in more widespread regions in the aged SHR, while LCBF was not significantly decreased in the aged WKY. The results indicate that, firstly, cerebral hypoperfusion is already established at the age of 4 months by persistent hypertension in SHR, but age-related decline of LCBF thereafter is not remarkable, and secondly, cerebral perfusion is preserved in normotensive WKY even in their senescence. Combined with the present results and the previous study that local cerebral glucose utilization (LCGU) reduced in the aged groups of WKY and SHR in scattered brain regions, more intensively and more extensively in the aged SHR, the followings are suggested: 1) in the young-adult SHR, LCBF is decreased but brain metabolism is preserved in a state of misery perfusion, 2) in the normotensive aged WKY, LCBF is preserved but brain metabolism is reduced implying "primary hypometabolism during senescence", and 3) in the aged SHR, LCBF is decreased and brain metabolism is more severely reduced, probably resulting from a combination of the primary hypometabolism of the brain by aging and a secondary hypometabolism due to the long-standing hypertension related hypoperfusion.

Introduction
It has been shown that changes in brain function during aging result from both primary neuronal degeneration associated with various morphological, neurotransmitter, and biochemical alterations, and secondary neuronal changes due to insufficient cerebral perfusion. Long-standing hypertension is known to cause functional and organic changes of arteries and arterioles including thickening of the wall, increased contractility, impaired dilatation, and altered reactivity. All these changes may lead to decreased cerebral perfusion. It seems clinically important to investigate the effects of long-standing hypertension on cerebral circulation, particularly during aging, because brain dysfunction secondary to inadequate cerebral perfusion may be prevented by controlling blood pressure.

Spontaneously hypertensive rats (SHR), a strain derived from Wistar-Kyoto rats (WKY), develop progressive hypertension with age, and are used widely in investigating cerebral hemodynamics. In our department, Mori et al. found that local cerebral glucose utilization (LCGU) in a number of discrete brain regions declined in the aged SHR more intensively and more widely than in age-matched normotensive WKY, although LCGU in young-adult SHR did not change compared with age-matched normotensive WKY, indicating that metabolic demand of the brain during aging is more decreased in hypertensive rats than in normotensive ones. These results, however, do not distinguish whether the reduced brain metabolism in the aged SHR is due to the primary neuronal loss during senescence or due to secondary process to decreased cerebral...
blood flow caused by the long-standing hypertension. The purpose of the present study, therefore, was to investigate any changes in local cerebral blood flow (LCBF) in SHR during aging, and to get a closer insight into the mechanism of the decreased brain metabolism of the aged SHR as shown by the decreased LGCU in the study of Mori et al.\textsuperscript{190}

Materials and methods

Animals

A total of 21 male rats of four groups with different ages and blood pressure were used: young-adult (4 months old) SHR and WKY groups, and aged (16-17 months old) SHR and WKY groups, with five rats in each group except aged SHR group, in which six rats were used. Okamoto-Aoki strain of SHR were raised in a specific-pathogen-free room of Kyushu University Animal Center, and WKY were purchased from Charles River Farms (Tosu City, Japan). All rats were housed in a 12:12 hour light-dark schedule (light on at 8:00) in an air conditioned room (24°C) and given free access to food and water. All rats used were treated humanely on the basis of the Public Health Service policy of the National Institutes of Health (1991). Table 1 shows physiological parameters of the animals. The aged WKY were significantly greater in body weight than the young-adult WKY (p<0.01). Although body weight of the aged SHR was significantly greater than that of the young-adult WKY (p<0.05), it was not significantly different from that of the young-adult SHR and was lighter than that of the aged WKY (p<0.01), indicating that the weight-gain in the aged SHR was not so marked as in the aged WKY.

Mean arterial blood pressure was significantly higher in the aged SHR than in WKY of both age groups (p<0.01) and in the young-adult SHR (p<0.05). The young-adult SHR tended to show higher blood pressure than WKY of both age groups, but this was not significant. The aged WKY showed similar blood pressure to that of the young-adult WKY.

Physiological parameters such as hematocrit, pH, PaO\textsubscript{2} and PaCO\textsubscript{2} were normal in the four groups, indicating that the assessment of LCBF was performed under similar physiological condition.

Local cerebral blood flow

Tables 2-4 show mean values for LCBF measured in 76 structures of the brain in the four groups of rats. The aged WKY showed lower LCBF rate in 60 out of 76 structures when compared with the young-adult WKY, with 12 structures showing more than 50% reduction. However, the difference was not statistically significant except for the substantia nigra pars reticulata and nucleus of the spinal tract of the trigeminal nerve (spinal V nucleus, compared with the young-adult WKY. The two age groups of SHR, on the other hand, showed significantly reduced LCBF in a
These structures, scattered widely throughout the young-adult substantia nigra pars compacta and reticulata, thalamic nuclei (Lateral geniculate nucleus), Basal ganglia (Hypothalamus), Lateral hypothalamic area (LHA), Striatum, Globus pallidus, Entopeduncular nucleus, Cingulate, Mediodorsal (MD), Ventromedial (VM), Ventralis lateralis (VL), Lateral dorsal (LD), Mediodorsal (MD), Paraventricular, Lateral geniculate nucleus, Mediodorsal nucleus, Lateral habenular nucleus, Hypothalamus (VMH), Ventromedial (VMH), Lateral hypothalamic area (LHA).

<table>
<thead>
<tr>
<th>Structures</th>
<th>WKY (n=5)</th>
<th>Aged (n=5)</th>
<th>SHR (n=5)</th>
<th>Aged (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral cortices</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>147.2 ± 25.1</td>
<td>149.1 ± 12.8</td>
<td>109.9 ± 6.7</td>
<td>109.3 ± 18.7</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>150.9 ± 25.0</td>
<td>134.6 ± 13.2</td>
<td>109.2 ± 4.4</td>
<td>114.6 ± 12.8</td>
</tr>
<tr>
<td>Parietal</td>
<td>139.4 ± 21.3</td>
<td>152.8 ± 28.1</td>
<td>124.6 ± 9.2</td>
<td>128.5 ± 18.1</td>
</tr>
<tr>
<td>Auditory</td>
<td>191.3 ± 26.9</td>
<td>192.9 ± 28.6</td>
<td>156.6 ± 22.3</td>
<td>154.9 ± 23.5</td>
</tr>
<tr>
<td>Visual</td>
<td>118.6 ± 13.0</td>
<td>116.9 ± 20.8</td>
<td>101.9 ± 12.9</td>
<td>103.9 ± 10.4</td>
</tr>
<tr>
<td>Cingulate</td>
<td>127.0 ± 19.0</td>
<td>132.2 ± 24.3</td>
<td>107.0 ± 13.6</td>
<td>107.0 ± 20.3</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striatum (dorsolateral)</td>
<td>114.0 ± 28.1</td>
<td>98.2 ± 12.7</td>
<td>71.4 ± 6.9</td>
<td>63.2 ± 9.5</td>
</tr>
<tr>
<td>(ventromedial)</td>
<td>96.7 ± 20.1</td>
<td>88.0 ± 17.3</td>
<td>63.7 ± 9.2</td>
<td>48.7 ± 7.8</td>
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<tr>
<td>Globus pallidus</td>
<td>62.8 ± 14.2</td>
<td>53.3 ± 6.9</td>
<td>40.7 ± 3.1</td>
<td>40.7 ± 9.1</td>
</tr>
<tr>
<td>Entopeduncular nucleus</td>
<td>50.7 ± 8.4</td>
<td>47.4 ± 6.4</td>
<td>37.0 ± 4.1</td>
<td>32.9 ± 2.0</td>
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<tr>
<td>Substantia nigra, pars compacta</td>
<td>78.4 ± 10.2</td>
<td>63.7 ± 4.9</td>
<td>59.9 ± 7.7</td>
<td>47.4 ± 9.0</td>
</tr>
<tr>
<td>pers reticulata</td>
<td>68.7 ± 9.4</td>
<td>52.7 ± 3.0</td>
<td>42.5 ± 8.6</td>
<td>37.3 ± 6.4</td>
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<tr>
<td>Subthalamic nucleus</td>
<td>115.6 ± 14.9</td>
<td>107.7 ± 13.0</td>
<td>91.1 ± 12.1</td>
<td>74.1 ± 15.7</td>
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<tr>
<td>Thalamic nuclei</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anteroventral(VA)</td>
<td>122.7 ± 73.1</td>
<td>119.5 ± 18.4</td>
<td>93.0 ± 18.9</td>
<td>90.0 ± 16.9</td>
</tr>
<tr>
<td>Ventromedial(VM)</td>
<td>106.9 ± 17.4</td>
<td>102.2 ± 13.5</td>
<td>79.2 ± 12.4</td>
<td>73.5 ± 15.6</td>
</tr>
<tr>
<td>Ventralis lateralis(VL)</td>
<td>113.5 ± 19.7</td>
<td>111.5 ± 12.0</td>
<td>90.1 ± 7.3</td>
<td>86.1 ± 18.3</td>
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<tr>
<td>Lateral dorsal(LD)</td>
<td>101.4 ± 10.7</td>
<td>100.4 ± 11.3</td>
<td>83.0 ± 6.9</td>
<td>82.4 ± 10.9</td>
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<tr>
<td>Mediodorsal(MD)</td>
<td>118.9 ± 72.1</td>
<td>114.0 ± 12.9</td>
<td>90.9 ± 9.3</td>
<td>95.2 ± 33.3</td>
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<tr>
<td>Paraventricular</td>
<td>82.6 ± 10.8</td>
<td>73.8 ± 8.6</td>
<td>68.8 ± 5.4</td>
<td>64.0 ± 12.4</td>
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<tr>
<td>Lateral geniculate nucleus</td>
<td>99.9 ± 18.2</td>
<td>89.7 ± 12.0</td>
<td>66.8 ± 8.6</td>
<td>62.7 ± 2.7</td>
</tr>
<tr>
<td>Mediodorsal nucleus</td>
<td>148.8 ± 21.7</td>
<td>133.6 ± 20.7</td>
<td>116.9 ± 22.3</td>
<td>112.8 ± 27.5</td>
</tr>
<tr>
<td>Lateral habenular nucleus</td>
<td>137.0 ± 20.8</td>
<td>136.0 ± 17.5</td>
<td>100.9 ± 23.6</td>
<td>111.6 ± 26.0</td>
</tr>
<tr>
<td>Hypothalamus (VMH)</td>
<td>68.4 ± 16.1</td>
<td>57.2 ± 11.2</td>
<td>54.0 ± 9.8</td>
<td>43.0 ± 10.1</td>
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<tr>
<td>Lateral hypothalamic area (LHA)</td>
<td>68.7 ± 16.9</td>
<td>64.2 ± 8.6</td>
<td>54.8 ± 9.6</td>
<td>47.7 ± 10.4</td>
</tr>
</tbody>
</table>

Values are mean ± SD (ml/100g/min).

* Highly significantly different from young-adult WKY (p < 0.05, *p < 0.01).
* Very significantly different from aged WKY (**p < 0.001).

Large number of the structures, compared with the young-adult WKY. In the young-adult SHR, LCBF was decreased in 18 out of 76 structures. These structures, scattered widely throughout the brain, included cerebral cortices (frontal and sensorimotor), basal ganglia (dorsolateral and ventromedial parts of striatum, globus pallidus, entopeduncular nucleus, and substantia nigra pars compacta and reticulata), thalamic nuclei (anteroventral and ventrolateral), lateral geniculate nucleus, limbic structures (posterior and entorhinal cortices), and lateral and medial septal nuclei, brainstem nuclei (inferior colliculus, red nucleus, ventral tegmental area, locus coeruleus, inferior olive and spinal V nucleus), cerebellum (flocculus and deep nuclei), and white matter (corpus callosum, fornix and internal capsule).

In the aged SHR, larger number of structures, 51 of 76 structures, showed significant reduction of LCBF compared with the young-adult WKY. All the structures where LCBF was decreased in the young-adult SHR also showed significant decline in LCBF except the locus coeruleus, in which LCBF decrease was not significant in the aged SHR. In additional 26 structures LCBF was reduced only in the aged SHR. These included basal ganglia (subthalamic nucleus), thalamic nucleus (ventromedial, laterodorsal and paraventricular nuclei), hypothalamus (ventromedial hypothalamic nucleus), limbic structures (dorsal hippocampus CA1, CA2, CA3 and dentate gyrus, basolateral nucleus of amygdala, and accumens), brainstem (interpeduncular nucleus, central gray, pontine reticular nucleus, pontine nucleus, raphé magnum, vestibular nucleus, cochlear nucleus, superior olive, cerebellum (hemisphere and vermal cortex). Significant LCBF decreases were also found in 28 structures of the aged SHR when compared with the young-adult WKY. All these structures also displayed significantly reduced LCBF in comparison with the young-adult WKY except two structures (mediodorsal nucleus of the thalamus and diagonal band). The aged SHR showed lower LCBF in 61 out
both SHR and WKY when compared with the respective young-adult groups, these flow reductions were not statistically significant.

The decreased LCBF in the young-adult SHR compared with the results of metabolic studies, which revealed that LCGU was not decreased in the young-adult SHR when compared with the young-adult WKY. Obo et al. revealed a decreased LCBF in the CA1 region of the hippocampus in stroke-prone SHR (SHRSP) of 4-5 months old when compared with SHRSRP of 2 months old. Although statistical comparison was not possible with WKY of 5 months of age because of a small number of animals in their study, the LCBF of the SHRSP of 4-5 months old showed clearly lower rates in the CA1 and tended to be lower in the caudate nucleus and thalamus. Yamori and Horie reported that LCBF measured by the hydrogen clearance method was greatly decreased in the frontal cortex of SHRSP at the age of 2-10 months than that of stroke-resistant SHR (SHRSRP) and WKY of comparable ages. In humans, PET studies revealed reduced cerebral blood flow in the supra- and infratentorial structures of hypertensive patients, even without cerebral infarction. All these findings are consistent with the results obtained in this study that LCBF decreases with persistent hypertension in animals. Wei et al. on the other hand, found no significant changes in LCBF between SHRSRP and WKY of 4-8 months old. Precise reasons for the discrepancy of the results are not known. Differences in level of hypertension, daily diet, other environmental factors, or experimental conditions may cause changes in hemodynamics, particularly in chronic animals. It has been known that long-lasting hypertension results in organic and functional changes of cerebral arteries and arterioles. It causes thickening of the arterial wall, which may develop within three weeks after experimentally induced renovascular hypertension in rats. Similar structural changes of the cerebral artery have been observed in SHR even as young as at the age of 15 days. Long-standing hypertension also causes increased contractility of arteries, impairment of arterial dilatation, disturbed arterial reactivity to CO, and impaired autoregulation of CBF. Also noted in SHR is an inherent defect of blood-brain barrier.

In the aged SHR, LCBF was decreased in larger numbers of the brain structures than in the young-adult SHR when compared with the young-adult WKY, indicating that the area of hypoperfusion extends in SHR during aging.

The present study of LCGU by Moroi et al. revealed that LCGU was not decreased in the young-adult SHR but decreased in the aged groups of SHR and WKY compared with respective young-adult age groups. Among the aged groups, LCGU reduction was more greatly and widely observed in the aged SHR than in the young WKY. Combined with these results, the present study indicates the following: Firstly, in the young SHR, brain atrophy and impaired regulation of arterial dilation is maintained in spite of the presence of decreased blood supply. Such flow-metabolism relation is called as "迷你perfusion". Thereby, the "normally active" neurons of the young-adult SHR take up as much oxygen and glucose as needed by increasing oxygen and glucose extraction rates. Similar phenomena have been observed even in young SHR, in which cerebral metabolic rate of oxygen (CMRO2) measured by PET was kept normal by increasing oxygen and glucose extraction rates in the presence of decreased LCBF in hypertensive patients. Secondly, the decreased LCGU with little reduction in LCBF in the aged WKY reflects a "primary hypometabolism" of the brain due to aging, which is not
caused secondarily by disturbed cerebral perfusion. Thirdly, the more profound and more wide-spread reduction in LCGU in the aged SHR than in the aged WKY results from combined causes of the primary hypometabolism due to aging and the secondary hypometabolism due to long-lasting hyperperfusion. These imply that, with long-standing hypertension, the secondary neuronal damage joins the primary one during aging, resulting in more extensive and more wide-spread brain hypometabolism.

Since hypertension can be treated with drugs, the secondary neuronal damage should be prevented by controlling hypertension. This is important because the brain function in aged may be better preserved by correcting blood pressure, thus maintaining cerebral perfusion adequately.

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