Effects of Acute Hypertension on Brain Metabolism in Normotensive, Renovascular Hypertensive and Spontaneously Hypertensive Rats

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SUMMARY Effects of angiotensin-induced acute hypertension on cerebral metabolism were studied in normotensive (NTR), spontaneously hypertensive (SHR) and experimental renovascular hypertensive rats (RHR).

Lactate, pyruvate and adenosine triphosphate (ATP) concentrations in the brain frozen in situ at 18–20 min after angiotensin infusion, which raised mean arterial pressure (MAP) by 28–62% of control, were determined by enzymatic methods. Supratentorial lactate was significantly increased to 135% of control in RHR, its increase being correlated with the increase in lactate/pyruvate ratio with a decrease in ATP despite no change of arterial acid-base balance measured simultaneously before and after acute induced hypertension.

From the present study, it is postulated that some renal factor seems to contribute ischemic metabolic changes in RHR following acute hypertension. The possible effect of renin on the vascular permeability is discussed as the pathogenesis of hypertensive encephalopathy.

THE PATHOGENESIS of hypertensive encephalopathy has not been fully understood. There have been 2 major contradictory theories proposed, 1 of which is intense arterial spasm in response to the rise in blood pressure with reduction of flow into the capillary bed resulting in ischemia, increased capillary permeability and cerebral edema. This was originally proposed by Oppenheimer and Fishberg,1 and was supported by Byrom’s in vivo observations of the pial circulation of renovascular hypertensive rats.2 The breakthrough or failure of autoregulation is another theory, which was recently proposed by Scandinavian investigators.3 They have demonstrated that breakthrough of the cerebral blood flow autoregulation occurs when blood pressure rises beyond a certain upper limit,4 resulting in an increase in cere-
bral blood flow, rise in capillary pressure, increased permeability, and finally cerebral edema. From the clinical standpoint, hypertensive encephalopathy seems to occur in hypertensive patients with renal involvement such as malignant hypertension, toxemia and acute nephritis rather than in those without, such as benign essential hypertension and primary aldosteronism. The appearance of symptoms of hypertensive encephalopathy usually follows acute onset of hypertension or a further rise in blood pressure in patients with already established hypertension. Cerebral edema has been described as the most common pathologic finding. It has been suggested that hypertension plus some unknown factor leading to increase in vascular permeability seems to lead to the development of hypertensive encephalopathy.

In the present study we measured glycolytic metabolites of the brain in 2 different models of hypertensive rats, in which blood pressure was further raised by angiotensin infusion. They included spontaneously hypertensive rats, a model of renin-independent benign hypertension, and experimental renovascular hypertensive rats, a model of renin-dependent hypertension which is able to progress to the malignant phase.

Materials and Methods

Production of Renovascular Hypertension

Male Wistar strain rats 2 months old, weighing 150–200 g, were anesthetized with intraperitoneal amobarbital (10 mg/100 g body weight). Through a dorsal incision, the left renal artery was exposed and constricted to 0.2 mm diameter by a silver clip. The contralateral kidney remained untouched. After operation, the animals were fed a regular diet and ad libitum tap water.

Blood pressure was measured weekly in the unanesthetized state by the tail-cuff technique. Only the animals in which systolic blood pressure was elevated to 160 mm Hg or above, were defined as RHR-high (RHR-H), and the remaining 15 RHR, of which MAP was below 160 mm Hg, were designated RHR-low (RHR-L). The relative heart weight was significantly greater in RHR-H than RHR-L as previously reported.

The body weight of the animals used was 344 ± 43

Results

Because of the effects of anesthesia, 30 RHR were divided arbitrarily into 2 groups; 15 RHR, of which mean arterial pressure (MAP) directly measured was 160 mm Hg or above, were defined as RHR-high (RHR-H), and the remaining 15 RHR, of which MAP was below 160 mm Hg, were designated RHR-low (RHR-L). The relative heart weight was significantly greater in RHR-H than RHR-L as previously reported.

The body weight of the animals used was 344 ± 43
g (mean ± s.d) in NTR, 317 ± 68 g in SHR, 286 ± 101 g in RHR-L and 241 ± 61 g in RHR-H, respectively. Its difference between NTR and RHR-H was significant (p < 0.005).

Blood Pressure and Arterial Acid-Base Balance

Maximal MAP after infusion of angiotensin was 181 mm Hg in NTR (50% increase from initial MAP), 214 mm Hg in SHR (28%), 190 mm Hg in RHR-L (62%) and 241 mm Hg in RHR-H (34%), respectively, as shown in table 1. In none of the animals did the MAP at the end of the experiment differ by 20 mm Hg more than from the initial level.

Arterial Pco2, Po2 and pH remained unchanged even after infusion, and did not differ between control and induced hypertensive rats of each group.

Brain Metabolites

Average values for supra- and infratentorial lactate, pyruvate, lactate/pyruvate (L/P) ratio and ATP are summarized in table 2.

After acute hypertension was induced, supratentorial lactate was significantly increased from 2.27 mM/kg control value to 3.07 mM/kg (135%, p < 0.05) in RHR-H, and from 1.77 mM/kg to 2.14 mM/kg (121%, p < 0.02) in RHR-L, while in either SHR or NTR, it remained unchanged. Figure 1 depicts the individual value of lactate in each group. Similarly, there was tendency for an increase in L/P ratio and a decrease in ATP in RHR-L and -H of the angiotensin group, but it did not reach statistical significance.

On the other hand, infratentorial lactate was in-

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of rats</th>
<th>MAP (mm Hg)</th>
<th>pH</th>
<th>Pco2 (mm Hg)</th>
<th>Po2 (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTR C</td>
<td>7</td>
<td>121 ± 9</td>
<td>7.413 ± 0.048</td>
<td>40.0 ± 2.7</td>
<td>83.3 ± 14.5</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>121 ± 17</td>
<td>7.382 ± 0.053</td>
<td>39.9 ± 5.8</td>
<td>83.2 ± 18.8</td>
</tr>
<tr>
<td>SHR C</td>
<td>7</td>
<td>170 ± 11</td>
<td>7.406 ± 0.026</td>
<td>40.2 ± 3.1</td>
<td>83.6 ± 17.6</td>
</tr>
<tr>
<td>A</td>
<td>7</td>
<td>168 ± 15</td>
<td>7.390 ± 0.068</td>
<td>40.3 ± 4.6</td>
<td>84.4 ± 17.7</td>
</tr>
<tr>
<td>RHR-L C</td>
<td>7</td>
<td>136 ± 15</td>
<td>7.407 ± 0.030</td>
<td>41.2 ± 3.1</td>
<td>84.4 ± 17.6</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>118 ± 14</td>
<td>7.393 ± 0.063</td>
<td>41.4 ± 5.0</td>
<td>81.5 ± 12.3</td>
</tr>
<tr>
<td>RHR-H C</td>
<td>7</td>
<td>177 ± 20</td>
<td>7.450 ± 0.070</td>
<td>37.7 ± 3.9</td>
<td>76.7 ± 5.9</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>180 ± 6</td>
<td>214 ± 25</td>
<td>7.435 ± 0.044</td>
<td>37.7 ± 3.6</td>
</tr>
</tbody>
</table>

NTR: normotensive rats; SHR: spontaneously hypertensive rats; RHR-L and -H: renovascular hypertensive rats of which MAP at the end of the experiment differ by 20 mm Hg or above (-H) under anesthesia; maximal: maximal MAP induced by angiotensin infusion. Values are mean ± s.d.

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of rats</th>
<th>Lactate (mM/Kg)</th>
<th>Pyruvate (mM/Kg)</th>
<th>L/P ratio</th>
<th>ATP (mM/Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTR C</td>
<td>6</td>
<td>1.67 ± 0.24</td>
<td>0.143 ± 0.044</td>
<td>12.5 ± 3.5</td>
<td>2.29 ± 0.28</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>1.78 ± 0.13</td>
<td>0.147 ± 0.035</td>
<td>12.8 ± 3.2</td>
<td>2.21 ± 0.48</td>
</tr>
<tr>
<td>SHR C</td>
<td>7</td>
<td>1.82 ± 0.19</td>
<td>0.137 ± 0.043</td>
<td>14.1 ± 3.1</td>
<td>2.14 ± 0.20</td>
</tr>
<tr>
<td>A</td>
<td>7</td>
<td>1.81 ± 0.24</td>
<td>0.190 ± 0.070</td>
<td>10.7 ± 3.9</td>
<td>2.27 ± 0.30</td>
</tr>
<tr>
<td>RHR-L C</td>
<td>6</td>
<td>1.77 ± 0.27</td>
<td>0.164 ± 0.030</td>
<td>11.1 ± 2.3</td>
<td>2.11 ± 0.35</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>2.14 ± 0.24**</td>
<td>0.153 ± 0.036</td>
<td>14.9 ± 5.7</td>
<td>2.03 ± 0.34</td>
</tr>
<tr>
<td>RHR-H C</td>
<td>7</td>
<td>2.27 ± 0.32</td>
<td>0.150 ± 0.025</td>
<td>15.5 ± 3.4</td>
<td>2.12 ± 0.32</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>3.07 ± 0.91*</td>
<td>0.165 ± 0.036</td>
<td>19.9 ± 9.2</td>
<td>1.93 ± 0.26 (5)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTR C</td>
<td>5</td>
<td>2.41 ± 0.50</td>
<td>0.176 ± 0.043</td>
<td>14.1 ± 3.8</td>
<td>2.19 ± 0.49</td>
</tr>
<tr>
<td>A</td>
<td>6</td>
<td>2.42 ± 0.27</td>
<td>0.167 ± 0.024</td>
<td>14.8 ± 2.6</td>
<td>1.93 ± 0.20</td>
</tr>
<tr>
<td>SHR C</td>
<td>6</td>
<td>2.37 ± 0.28</td>
<td>0.144 ± 0.057</td>
<td>18.0 ± 5.1</td>
<td>2.14 ± 0.36 (5)</td>
</tr>
<tr>
<td>A</td>
<td>7</td>
<td>2.50 ± 0.43</td>
<td>0.161 ± 0.045</td>
<td>16.3 ± 4.3</td>
<td>2.08 ± 0.28</td>
</tr>
<tr>
<td>RHR-L C</td>
<td>7</td>
<td>2.51 ± 0.29</td>
<td>0.133 ± 0.031</td>
<td>19.2 ± 3.8</td>
<td>1.87 ± 0.33</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>2.82 ± 0.73</td>
<td>0.148 ± 0.047</td>
<td>20.8 ± 5.3</td>
<td>1.83 ± 0.19 (6)</td>
</tr>
<tr>
<td>RHR-H C</td>
<td>7</td>
<td>2.44 ± 0.35</td>
<td>0.158 ± 0.043</td>
<td>16.2 ± 4.3 (6)</td>
<td>1.89 ± 0.21 (6)</td>
</tr>
<tr>
<td>A</td>
<td>8</td>
<td>3.45 ± 0.84**</td>
<td>0.171 ± 0.048</td>
<td>21.1 ± 5.4</td>
<td>1.87 ± 0.29 (6)</td>
</tr>
</tbody>
</table>

L/P ratio: lactate/pyruvate ratio. Values are mean ± s.d. Number in the parenthesis denotes number of rats. Statistical significance between control and acute hypertension as *p < 0.05, **p < 0.02.
increased to 141% of control in only RHR-H after acute hypertension, its difference being significant ($p < 0.02$). Otherwise, there was no change in infratentorial metabolites between the control and experimental animals of each group.

**Relationship Between Lactate and Blood Pressure**

Figure 2 demonstrates the relationship between supratentorial lactate and the initial MAP of control rats or maximal MAP of experimental ones in NTR and SHR, and figure 3 in RHR-L and RHR-H. In the former, lactate was constant despite the wide range of blood pressure, while in the latter, its correlation was highly significant ($r = 0.721$, $p < 0.001$), indicating that supratentorial lactate was increased more as blood pressure was raised in RHR.

**Discussion**

There have been a great number of clinical as well as experimental studies on the pathogenesis of hypertensive encephalopathy. Acute hypertension induced by various vasoactive agents or by compression of the descending aorta leads to either blood-brain barrier (BBB) dysfunction resulting in the extravasation of protein and ultrastructural changes, or to forced vasodilatation resulting in increased cerebral blood flow, although there were contradictory observations. In a series of experimental studies by Johansson and coworkers, acutely induced hypertension caused increased permeability due to vascular distension and extravasion of protein. Such phenomena are exaggerated by pretreatment with vasodilators such as papaverine and hypercapnea or bicuculline-induced seizures, whereas they are prevented by hypocapnic vasoconstriction or persistent vasoconstriction as seen in SHR. There was no report on RHR.

In contrast to the numerous physiological and morphological studies, only Johansson and Siesjö have recently described the effects of acute hypertension on brain metabolism. They found that angiotensin-induced hypertension in NTR did not affect the tissue metabolites as lactate, L/P ratio and high energy phosphate compounds, although these animals showed multi-focal areas of Evans blue-albumin leakage of the brain. They interpreted the absence of ischemic metabolic changes, as contradicting the hypothesis that acute hypertension causes vasospasm and ischemia resulting in disturbance of permeability or breakdown of BBB.

The present study showing that neither lactate nor ATP was affected by acute hypertension in normotensive animals is compatible with results obtained by Johansson and Siesjö. Similarly, such metabolic changes were not evident in SHR. In renovascular hypertension, meanwhile, a further induced elevation of blood pressure by 60–70 mm Hg did cause a slight but significant increase in cerebral lactate, its increase being correlated with the magnitude of blood pressure.
rise. Increased lactate by an average 0.8 mM/kg (35% of control) in RHR-H, and 0.37 mM/kg (21%) in RHR-L after acute hypertension seems to be comparable with the metabolic changes resulted from approximately 50% reduction of cerebral blood flow in rats.\(^\text{20, 24}\) Besides an increase in lactate, the L/P ratio tended to increase and ATP to decrease in these rats, these being sensitive indicators of brain ischemia.

From the present study, however, it is not clear whether the metabolic changes are primarily due to the reduction of cerebral blood flow or secondarily due to the increased permeability that causes brain edema resulted in lowering of blood flow.

Renovascular hypertension is renin-dependent, while SHR hypertension is genetically determined and not related to the renin-angiotensin system. Based on other studies, it seems possible that renin itself, or some product determined by it ("vasculotoxin") increases vascular permeability and results in vasculopathy.\(^\text{26}\) Brunner et al.\(^\text{26}\) have shown that high-renin hypertension in humans leads more frequently to vascular complications including stroke and myocardial infarction.

Our present study fits well with these previous reports: significant increases in lactate following acute transient hypertension occurred only in renin-dependent hypertensive rats and not in normotensive or genetically hypertensive rats suggesting that some renal factor in addition to the abrupt rise of blood pressure is important in causing ischemic metabolic changes in the brain.

Acknowledgment

The authors wish to thank Miss Yohko Sonoda, Miss Yuriko Fujino, and Miss Mayumi Taki for technical assistance, and Miss Junko Hirakawa for preparing this manuscript.

References

Effects of acute hypertension on brain metabolism in normotensive, renovascular hypertensive and spontaneously hypertensive rats.
M Fujishima, K Onoyama, H Oniki, J Ogata and T Omae

Stroke. 1978;9:349-353
doi: 10.1161/01.STR.9.4.349

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