Modification of Cerebrovascular CO₂ Reactivity by Inhibition of Dopamine β-Hydroxylase

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SUMMARY The influence of sympathetic nervous activity on cerebral circulation and cerebrovascular CO₂ reactivity was investigated through inhibition of dopamine β-hydroxylase (DBH). A PO₂ electrode, a PCO₂ electrode and a plate-type thermocouple-flowmeter were placed on the pial surface of the cat brain. Cerebrocortical PO₂, PCO₂, cerebrocortical blood flow and arterial blood pressure were continuously recorded before, during and after intracarotid infusion of 10 mg/kg of fusaric acid, a potent DBH inhibitor. The effects of 5% CO₂ inhalation and hyperventilation were measured before and after the inhibition of DBH. Following the intracarotid infusion of fusaric acid, cerebrocortical PO₂ and cerebrocortical blood flow increased significantly. After the inhibition of DBH, the degree of the increase in cerebrocortical PO₂ during 5% CO₂ inhalation was enhanced while the degree of the decrease in cerebrocortical PO₂ during hyperventilation did not show any significant change. The cerebrovasodilatation caused by fusaric acid suggests that the sympathetic nervous system modifies cerebrovascular CO₂ reactivity. Stroke Vol 10, No 4, 1979

CEREBRAL BLOOD VESSELS have been found to be richly innervated with sympathetic nerve fibers,⁹ which appear to be most dense in the larger arteries.³ Dopamine β-hydroxylase (DBH), the final enzyme in the biosynthesis of norepinephrine, exists in the adrenal medulla, the brain, and various sympathetically innervated organs including cerebral arteries.²,⁴ In some conditions with an increased sympathetic discharge,² a high serum DBH level is considered to be due to an increased release of DBH from sympathetic nerve terminals. Since the influence of inhibition of DBH on cerebral circulation and cerebrovascular CO₂ reactivity has not yet been reported, it was investigated.

Materials and Methods

Nine cats weighing 2.8–4.8 kg were anesthetized with intraperitoneal pentobarbital sodium (40 mg/kg) and regional procaine hydrochloride. Polyethylene catheters were placed in a femoral artery for continuous recording of blood pressure and in the right lingual artery for infusion of the drug into the right carotid artery. After tracheostomy, the animals were immobilized with alcuronium chloride and a tracheal cannula was connected to a variable-speed respirator pump (Type NSH-34RH, Harvard Apparatus Co.). The respira-
tory rate was set to 20 strokes/min and the stroke volume set to between 30–45 ml depending on the size of the animal. The pial surface of the right cerebral cortex was exposed by removing the overlying skull and dura mater. A Po2 electrode, a Pco2 electrode and a plate-type thermocouple-flowmeter (Type P-3LH, Unique Medical Co.) were placed on the cortex by means of adjustable rods with springs. The Po2 electrode consisted of a platinum cathode and a silver-silver chloride anode and Po2 is measured by the polarographic principle. The principle of the method for measuring Pco2 is based on the change in the pH of a weak bicarbonate solution enclosed within a Teflon membrane when it is diffused by CO2 from outside the membrane. The animal's head was covered with a vinyl tent and the temperature of the cerebral cortex was checked with a thermister to remain constant. Data were recorded continuously on an ink-writing polygraph (Electronic Recorder Model B-341, Rika Denki Co.).

Arterial blood Po2, Pco2 and pH were measured with a blood gas analyzer (Acid-Base Analyzer PHM 71, Radiometer Co.) before and after the administration of fusaric acid, a DBH inhibitor in 9 cats.

With an infusion pump 10 mg/kg of fusaric acid, dissolved in 1 ml saline solution (pH = 3.50), was infused into the carotid artery over 5 min, and after saline solution was infused at the same speed. Inhalation of 5% CO2 + air for 2 min and hyperventilation (respiratory rate was increased from 20 to 40 strokes/min for 2 min) were accomplished before and after the intracarotid infusion of fusaric acid. The results were expressed as means ± standard deviation and the statistical significance was judged on the basis of Student’s t-test.

Results

1) Effects of Intracarotid Infusion of Fusaric Acid on Cerebral Circulation

Figure 1 is an actual polygraphic record of the changes in each parameter before, during, and after the intracarotid infusion of fusaric acid.

Cerebrocortical Po2 and cerebrocortical blood flow started to increase shortly after the beginning of the infusion and returned gradually to their initial level in 20 min.

Similar results were obtained in 9 cats and the changes in each measurement during the 16 min from the beginning of the infusion are summarized in figure 2. Following the intracarotid infusion of fusaric acid, cerebrocortical Po2 and cerebrocortical blood flow increased significantly without a significant change in cerebrocortical Pco2 or mean arterial blood pressure. Arterial blood Po2, Pco2 and pH (table 1) were not changed significantly by the infusion of fusaric acid.

2) Effects of 5% CO2 Inhalation Before and After Inhibition of DBH

Table 2 compares the changes in each parameter during 5% CO2 inhalation before and after the inhibi-
CO₂ Reactivity After DBH Inhibition/Oishi et al.

Therefore, the cerebral vasodilatation observed is before and after the Intracarotid Infusion of Fusaric Acid in 9 cats. After the infusion, the degree of decrease in cerebrocortical PaO₂ and cerebrocortical blood flow was reduced as compared with that before the infusion but this change was not statistically significant.

Table 1: Comparison of Arterial Blood PaO₂, PaCO₂ and pH before and after the Intracarotid Infusion of Fusaric Acid in 9 Cats

<table>
<thead>
<tr>
<th></th>
<th>PaO₂ (mm Hg)</th>
<th>PaCO₂ (mm Hg)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>98.2 ± 7.0*</td>
<td>39.1 ± 4.5</td>
<td>7.391 ± 0.047</td>
</tr>
<tr>
<td>After</td>
<td>97.8 ± 7.1</td>
<td>39.2 ± 4.6</td>
<td>7.388 ± 0.054</td>
</tr>
<tr>
<td>∆</td>
<td>-0.4 ± 3.7</td>
<td>0.1 ± 0.5</td>
<td>-0.003 ± 0.023</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation.

cerebrocortical PaCO₂ or mean arterial blood pressure before and after the inhibition of DBH.

3) Effects of Hyperventilation Before and After Inhibition of DBH

Table 3 compares the changes in each area during hyperventilation before and after the infusion of fusaric acid in 9 cats. After the infusion, the degree of decrease in cerebrocortical PaO₂ and cerebrocortical blood flow was reduced as compared with that before the infusion but this change was not statistically significant.

**Discussion**

In this study the intracarotid infusion of fusaric acid caused significant increases in cerebrocortical PaO₂ and cerebrocortical blood flow with no significant change in blood pressure or arterial blood gases. These data indicate a cerebral vasodilatation. The cerebral vasodilatation is attributable not to the acidity of the solution but to the specific action of fusaric acid, since intracarotid infusion of hydrochloric acid solution with the same pH at the same speed did not cause any significant change.

Although cerebrocortical PaCO₂ occasionally showed a slight increase initially, this degree of change was not sufficient to explain the definite increase in cerebrocortical PaO₂ and cerebrocortical blood flow. Therefore, the cerebral vasodilatation observed is believed to be due to the inhibition of DBH rather than to an increase in cerebral metabolism, though the possibility that fusaric acid may have a direct cerebral vasodilating action cannot be excluded. The cerebral vasodilatation produced by the inhibition of DBH suggests that the sympathetic nervous system plays a role in maintaining the resting tone of cerebral vessels.

The influence of the sympathetic nervous system on cerebrovascular CO₂ reactivity has been examined through section of the cervical sympathetic nerves, administration of 6-hydroxydopamine, an α-blocker, or a β-blocker, but the results of these studies are conflicting. Supersensitivity produced by superior cervical sympathectomy may cause some difference between acute and chronic experiments. Cerebral arteries in parts of the brain might be innervated by both the cervical sympathetic nerve and central noradrenergic neurons. An α-blocker decreases blood pressure and a β-blocker decreases cerebral metabolism. In order to avoid these problems, the inhibition of DBH was employed as a means to suppress sympathetic nervous activity in our study, and the inhibitor, fusaric acid, was infused into the carotid artery to minimize its effect on blood pressure.

After the inhibition of DBH, the degree of increase in cerebrocortical PaO₂ during 5% CO₂ inhalation was enhanced significantly without a significant change in the degree of the increase in cerebrocortical PaCO₂ or mean arterial blood pressure. This observation indicates an increase in the cerebrovascular CO₂ reactivity. The mechanism of the increase in cerebrovascular CO₂ reactivity after suppression of sympathetic nervous system activity is uncertain. Cerebrovascular CO₂ reactivity and autoregulation of the cerebral circulation are considered to be influenced by different mechanisms because there are dissociations between the two. From the observation that the smaller arteries with coarse or no sympathetic innervation respond to changes in PaCO₂ and and that the larger arteries with dense innervation respond to changes in blood pressure, Gotoh et al. postulated a dual control of the cerebral circulation which consists of chemical control functioning in the cerebrovascular response to local metabolic needs or to blood gas changes and neurogenic control operating in autoregulation.

Our finding that the cerebrovascular CO₂ reactivity was increased after the inhibition of DBH might be explained in 3 ways: 1) The vasodilatation of the larger arteries produced by the inhibition of DBH causes a compensatory vasoconstriction of the smaller arteries through chemical control, therefore the cerebrovascular CO₂ reactivity is increased. 2) The smaller arteries dilate through chemical control with 5% CO₂ inhalation, while the larger arteries constrict through neurogenic control because of the hypertension induced by 5% CO₂ inhalation, as this vasoconstriction is suppressed by the inhibition of DBH, the cerebrovascular CO₂ reactivity is increased. 3) The direct cerebral vasodilating action of CO₂ is accompanied by a sympathetic vasoconstricting action as in the skin, though this sympathetic vasoconstriction is much weaker in the brain than in the skin, so the in-

Table 2: Effects of 5% CO₂ Inhalation on Cerebrocortical PaO₂ (BrPaO₂), Cerebrocortical PaCO₂ (BrPaCO₂), Cerebrocortical Blood Flow and Mean Arterial Blood Pressure before and after the Inhibition of DBH in 9 Cats

<table>
<thead>
<tr>
<th></th>
<th>∆BrPaO₂ (mm Hg)</th>
<th>∆BrPaCO₂ (mm Hg)</th>
<th>∆CBF (V)</th>
<th>∆MABP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>7.1 ± 3.9</td>
<td>9.8 ± 4.4</td>
<td>11.5 ± 6.8</td>
<td>9.2 ± 8.5</td>
</tr>
<tr>
<td>After</td>
<td>11.9 ± 6.0</td>
<td>10.1 ± 4.8</td>
<td>18.1 ± 10.2</td>
<td>9.8 ± 11.0</td>
</tr>
<tr>
<td>∆</td>
<td>4.8 ± 5.5*</td>
<td>0.3 ± 1.9</td>
<td>6.6 ± 9.4</td>
<td>0.6 ± 6.9</td>
</tr>
</tbody>
</table>

*Statistically significant (p < 0.05).
hibitation of DBH increases cerebrovascular CO2 reactivity.

References


### TABLE 3 Effects of Hyperventilation on Cerebrocortical Pco2 (BrPco2), Cerebrocortical Pco2 (BrPco2), Cerebrocortical Blood Flow and Mean Arterial Blood Pressure before and after the Inhibition of DBH in 8 Cats

<table>
<thead>
<tr>
<th></th>
<th>BrPco2 (mm Hg)</th>
<th>BrPco2 (mm Hg)</th>
<th>CBF (mL/min)</th>
<th>MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>-9.1 ± 2.5</td>
<td>-8.1 ± 3.0</td>
<td>-18.8 ± 9.1</td>
<td>-6.3 ± 5.1</td>
</tr>
<tr>
<td>After</td>
<td>-6.8 ± 2.8</td>
<td>-8.6 ± 3.7</td>
<td>-14.1 ± 10.6</td>
<td>-5.8 ± 5.5</td>
</tr>
<tr>
<td>∆</td>
<td>2.3 ± 3.6</td>
<td>-0.5 ± 3.0</td>
<td>4.7 ± 6.9</td>
<td>0.6 ± 4.8</td>
</tr>
</tbody>
</table>

Before

-6.8 ± 2.8

-9.1 ± 2.5

-14.1 ± 10.6

-6.3 ± 5.1

-5.8 ± 5.5

4.7 ± 6.9

0.6 ± 4.8
Cerebral Artery Thrombosis and Intramural Hemorrhage

SEIZO SADOSHIMA, M.D., TAKEO FUKUSHIMA, M.D., AND KENZO TANAKA, M.D.

SUMMARY Thirty-nine thrombosed arterial segments of the branches of the circle of Willis were studied by a complete serial section technique. Twenty-two patients had been hypertensive and 8 had hypercholesterolemia before the onset of cerebral artery thrombosis. The histological characteristics of the thrombosed arterial segments were intramural hemorrhage in 28 segments, superficial edema of the fibrous cap of the atheroma or fibrous plaque in 4, rupture of the atheromatous plaque in 1, superficial accumulation of foam cells in the atheroma in 1 and an atheroma or fibrous plaque of 22 segments with intramural hemorrhage. Fibrinoid degeneration of these small blood vessels was noted in 5. These findings suggested that intramural hemorrhage from the intramural small blood vessels was the major cause of cerebral artery thrombosis and that persistent hypertension not only promoted cerebral atherosclerosis but also induced hemorrhage from the intramural small blood vessels.

CEREBRAL ARTERY THROMBOSIS is one of the major causes of death among Japanese. It is usually not clear what kind of pathologic processes participated in cerebral artery thrombosis.

In the pathogenesis of coronary artery thrombosis, rupture or fissure formation of an atherosclerotic plaque has generally been considered to be a major cause of thrombus precipitation, but only a few investigators have suggested that intramural hemorrhage initiated the process leading to thrombosis. No agreement exists on the mechanism of occlusive thrombosis in cerebral arteries. Some consider that it is caused by a break or ulceration of the atherosclerotic intima similar to that in coronary artery thrombosis, and others believe that it is initiated by hemorrhage from intramural capillaries.

The histologic characteristics of the wall of thrombosed cerebral arteries were studied in 39 freshly occluded branches of the circle of Willis after a complete serial section.

Material and Methods

Thirty-three autopsied cases of cerebral artery thrombosis were investigated. The patients died within 4 weeks after the onset of cerebral apoplexy and were admitted during 1964 to 1974 at the hospitals of Kyushu University, Kurume University and Kawasaki University and other hospitals. As more than 2 thrombi were found in 4 cases, 39 thrombosed arterial segments were submitted for examination. Twenty-four thrombi were found in the middle general artery, 6 in the vertebral, 4 in the internal carotid, 2 in the posterior, 1 in the anterior cerebral, 1 in the posterior inferior cerebellar and 1 in the basilar artery.

The 33 patients included 23 men and 10 women, and their ages ranged from 43 to 89 years. The average age was 69 years, 2 months. The elapsed time between the onset of symptoms and death was ascertained. Twenty-two of 29 patients whose blood pressure was measured before the onset of apoplexy remained hypertensive according to the criteria of the World Health Organization. The total serum cholesterol level was 250 mg/100 ml or more in 8 of 24 patients examined. In none of the patients were thromboemboli found in the hearts, aortas or carotid arteries.

The occluded arterial segments, including proximal and distal non-occluded areas, were removed and fixed in 10% neutral formalin. The entire arterial specimen was cut serially in segments 5 μm thick, from the beginning to end of the occluded arterial portion. Five to 10 sections were mounted on each slide and stained with hematoxylin and eosin, and elastica Van Gieson in turn. Alcian-blue PAS stain and Berlin-blue stain were used when needed.

Results

The original lumina in 25 of the 39 segments was narrowed 50% or more by atheromatous or fibrous plaques. Calcification was present in only 4 segments.
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M Oishi, F Gotoh, M Toyoda, T Seki, T Takeoka, S Takagi and T Niimi

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