demonstration using tranylcypromine, a similar demonstration by others, and a direct demonstration in which PGJ_2 was locally applied to injured vessels in hamster cheek pouch. Our data thus offer a different type of supporting evidence on the capacity of PGJ_2 to influence platelet aggregation in vivo. We have, in addition, extended previous data to another organ and another species, suggesting that PGJ_2 modulation of platelet function is a widespread phenomenon.

Acknowledgment

Ms. Anne Litten provided essential technical assistance. PGJ_2 supplied by Dr. John E. Pike, The Upjohn Co., Kalamazoo, MI.

References

1. Gryglewski RJ, Bunting S, Moncada S, Flower RJ, Vane JR: Arterial walls are protected against deposition of platelet thrombi by a substance (prostaglandin X) which they make from prostaglandin endoperoxides. Prostaglandins 12:685-713, 1976
2. Moncada S, Gryglewski RJ, Bunting S, Vane JR: A lipid peroxide inhibits the enzyme in blood vessel microsomes that generates from prostaglandin endoperoxides the substance (Prostaglandin X) which prevents platelet aggregation.

Effect of Phenoxybenzamine on Cerebral Blood Flow and Metabolism in the Baboon During Hemorrhagic Shock

JÁNOS HAMAR, M.D., ARISZTID G. B. KOVÁCH, M.D., MARTIN REIVICH, M.D., ISTVÁN NYÁRY, M.D., AND FELIX DURITY, M.D.

SUMMARY Experiments were performed on 2 groups of baboons anesthetized with Sernylan. One group served as control and the other was premedicated with 5 mg/kg phenoxybenzamine (PBZ). A 2-step hypovolemic shock model was used followed by retransfusion of the shed blood. Cerebral blood flow was measured by the 188Xe clearance method. Arterial and cerebral venous samples were taken and analyzed for blood gases as well as glucose and lactate content. The cerebral metabolic rates of oxygen, glucose, and lactate were calculated. In addition, the effect of CO_2 inhalation was studied before shock was induced. PBZ produced no effect on either CBF or the flow response to CO_2 prior to bleeding. PBZ pretreatment prevented the fall in cerebral blood flow and CMRO2 produced by systemic hypotension due to bleeding. Lactic acid showed no evidence of change either in production or uptake by the brain during the experimental procedure. The cerebral metabolic pathway of glucose, however, seemed to be affected by PBZ both before and during shock.

PHENOXYBENZAMINE (PBZ) has a beneficial effect on various forms of shock. It has been demonstrated that the tissue blood flow to different organs was improved and metabolic changes induced by shock were reduced or abolished by pretreatment with phenoxybenzamine.

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It is generally assumed that owing to its well-developed autoregulation of blood flow, the brain's vital functions are protected during hypotension and shock. However, it has been demonstrated that the EEG and evoked potentials disappear during hypovolemia and do not return after reinfusion. In addition, metabolic and functional alterations occur which lend support to the concept that the central nervous system (CNS) is seriously affected in shock. Earlier studies in dogs showed that blood flow in different regions of the brain did not decrease to the same extent after PBZ premedication and the electrical activity of the cortex seemed to be preserved.

Because earlier studies with PBZ in shock were per-
formed on subprimate species and, more recently, cerebral blood flow and metabolism were found to be seriously affected by hemorrhagic shock in the baboon.\textsuperscript{11, 12} We studied the effect of PBZ pretreatment on tissue blood flow and metabolism in the brain of the baboon during hemorrhagic shock.

**Methods**

Five control and 5 PBZ pretreated baboons of either sex (weight 10–15 kg) were studied. They were initially anesthetized with 1 mg/kg Sernylan (Bio-Ceutic Laboratories Inc., St. Joseph, MO) and subsequently given 0.3 mg/kg each hour.

The left femoral artery and vein were cannulated and used for bleeding and for the administration of systemic medication. The right brachial artery was cannulated for blood pressure monitoring and blood sampling. A thin polyethylene catheter was introduced into the left lingual artery for the injection of 133Xe (Cambridge Nuclear Radiopharmaceutical Corporation, Princeton, NJ). The external carotid artery was ligated immediately distal to the lingual artery origin.

The head was fixed in a stereotaxic headclamp with the animal in the prone position. Flaxedil, 1.5 mg/kg (Davis & Geck, American Cyanamid Co., Pearl River, NY) was given intravenously and artificially ventilated (dual pulse control respiration pump, Harvard Apparatus, Willis, MA) instituting using a gas mixture of 30% O\textsubscript{2} in N\textsubscript{2}. End-tidal P\textsubscript{CO\textsubscript{2}} was continuously monitored by an infrared CO\textsubscript{2} analyzer (Beckman medical gas analyzer, Beckman Instrument Inc., Fullerton, CA). Maintenance doses of Flaxedil were given as required.

The skin and muscles over the left hemicranium were removed using an electrocautery. The posterior part of the sagittal sinus was exposed through a 1.5 cm burr hole and cannulated for venous pressure monitoring. A second polyethylene catheter was introduced into the left lingual artery for the injection of 133Xe. The skin and muscles overlying the frontal, parietal and occipital lobes for electroencephalographic (EEG) recording (Model 6 EEG, Grass Instrument Co., Quincy, MA).

Phenoxybenzamine (Dibenzyline, Smith Kline & French Laboratories, Philadelphia PA), 5 mg/kg dissolved in a 50% mixture of ethyl alcohol and saline at a final concentration of 25 mg/ml, was injected intravenously over a period of 10 min, 3 hours before the experimental procedure. To avoid a sudden drop of blood pressure, saline (100–150/50 ml) was slowly infused during the injection of the PBZ. The animals were heparinized (2 mg/kg).

Cerebral blood flow (CBF) was measured using the intracarotid 133Xe clearance method.\textsuperscript{13, 14} Eight collimated NaI (TI) crystals were closely applied to the skull overlying the frontal, parietal and temporoparietal lobes.

Mean cerebral blood flow (MCBF) was calculated as the arithmetic mean of the 8 regional mean flows. A biexponential analysis of each clearance curve was performed and values for fast (gray matter) and slow (white matter) flow components, along with their weights, were calculated.

Glucose and lactate concentrations in arterial and cerebrovenous blood samples were determined according to the methods of Bergmeyer.\textsuperscript{15} The PO\textsubscript{2}, P\textsubscript{CO\textsubscript{2}}, pH and O\textsubscript{2} saturation as well as hemoglobin (Hb) concentration of the samples were also determined (AMT-I blood gas analyzer, Radiometer, Copenhagen and Co-oxymeter Model 182, Instrumentation Laboratories Inc., Lexington, MA).

The cerebral metabolic rates (CMR) for glucose and O\textsubscript{2} were calculated from the mean blood flow values and the arteriovenous differences for glucose and O\textsubscript{2}, respectively. Cerebrovascular resistance (CVR) was calculated using the formula:

\[
CVR = \frac{MABP-CVP}{MCBF}
\]

where MABP = mean arterial blood pressure and CVP = cerebral venous pressure. Paired r-tests were used for statistical evaluation.

**Experimental Protocol**

After a control CBF measurement (flow #1) was obtained with the animal breathing 30% O\textsubscript{2} in N\textsubscript{2}, the baboon was ventilated with a gas mixture of 5% CO\textsubscript{2} and 30% O\textsubscript{2} in N\textsubscript{2} and a second CBF determination (flow #2) was made to test the reactivity of the cerebral vessels to CO\textsubscript{2}. A third CBF measurement was performed (flow #3) after returning to the initial inhalation gas mixture. The animals were then bled into a buffer reservoir over 10 min and the mean arterial blood pressure was maintained at 55 mm Hg for 90 min during which 3 more CBF determinations were performed (Bleeding 1 (Bl) flows #4, 5, 6). Following Bl the mean arterial blood pressure was reduced to and maintained at 35–40 mm Hg for an additional 90 min during which 3 additional CBF determinations were performed (B2 flows #7, 8, 9). After B2 the blood from the buffer reservoir was retransfused. Thirty minutes later, when BP and end-tidal P\textsubscript{CO\textsubscript{2}} were stabilized, CBF was again measured (flow #10).

**Results**

**Control Studies (Table 1)**

MABP was altered according to the method described. It was significantly less after retransfusion when compared to control values.

MCBF was only slightly depressed during Bl but it significantly decreased from a control value of 39.4 to 21.9 ml/100 g/min by the end of B2. MCBF rose to 78.7 ml/100 g/min after retransfusion. CVR was significantly lower during hemorrhage and after retransfusion compared to the prebleeding value.

Arterial P\textsubscript{CO\textsubscript{2}} continuously decreased from a control value of 36.7 mm Hg to 25.7 mm Hg by the end of B2. Systemic arterial and cerebral venous pH values also gradually decreased throughout Bl, B2 and after retransfusion.

The bleeding volume reached its highest level (18.8 ml/kg B.W.) at the 60th min of Bl. There was a spon-
PBZ EFFECT IN SHOCK/Hamar et al.

TABLE 1  Cerebral Hemodynamic and Metabolic Changes in the Baboon in Hemorrhagic Shock

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Bleeding 1</th>
<th>Bleeding 2</th>
<th>Retransfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30'</td>
<td>60'</td>
<td>90'</td>
<td>60'</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>112.0±9.3</td>
<td>112.0±9.4</td>
<td>112.0±9.2</td>
<td>112.0±9.4</td>
</tr>
<tr>
<td>Art. pCO₂ (mm Hg)</td>
<td>39.9±4.4</td>
<td>39.9±4.4</td>
<td>39.9±4.4</td>
<td>39.9±4.4</td>
</tr>
<tr>
<td>CVR</td>
<td>2.98±0.4</td>
<td>2.98±0.4</td>
<td>2.98±0.4</td>
<td>2.98±0.4</td>
</tr>
<tr>
<td>Art. pH</td>
<td>36.7±1.95</td>
<td>36.7±2.07</td>
<td>36.7±2.07</td>
<td>36.7±2.07</td>
</tr>
<tr>
<td>Ven. pH</td>
<td>7.388±0.033</td>
<td>7.388±0.032</td>
<td>7.388±0.032</td>
<td>7.388±0.032</td>
</tr>
<tr>
<td>Shed blood (ml/kg b.w.)</td>
<td>17.1±2.07</td>
<td>18.8±2.84</td>
<td>16.8±2.20</td>
<td>16.7±2.49</td>
</tr>
<tr>
<td>MCBF (ml/100 g/min)</td>
<td>4.47±0.30</td>
<td>4.47±0.74</td>
<td>4.47±0.95</td>
<td>4.47±0.23</td>
</tr>
<tr>
<td>CMRO₂ (ml/100 g/min)</td>
<td>3.93±0.35</td>
<td>3.93±0.23</td>
<td>3.93±0.38</td>
<td>3.93±0.38</td>
</tr>
</tbody>
</table>

*Numbers represent the mean of 5 experiments ± SE.

Significant differences compared to control animals without premedication.

PBZ EFFECT IN SHOCK/Hamar et al.

TABLE 2  Cerebral Hemodynamic Parameters in the Baboon Pretreated with Phenoxybenzamine†

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control CO₂</th>
<th>Bleeding 1</th>
<th>Bleeding 2</th>
<th>Retransfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30'</td>
<td>60'</td>
<td>90'</td>
<td>60'</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>92.5±7.2</td>
<td>100.0±4.7</td>
<td>88.0±5.8</td>
<td>55.0±5.4</td>
</tr>
<tr>
<td>Ven. press. (mm Hg)</td>
<td>45.0±3.0</td>
<td>33.0±5.1</td>
<td>6.8±2.5</td>
<td>7.2±2.5</td>
</tr>
<tr>
<td>Per fus. press. (mm Hg)</td>
<td>77.5±8.0</td>
<td>67.0±4.4</td>
<td>81.2±2.4</td>
<td>48.2±4.8</td>
</tr>
<tr>
<td>MCBF (ml/100 g/min)</td>
<td>48.2±3.6</td>
<td>79.4±1.97</td>
<td>37.4±1.38</td>
<td>41.9±5.16</td>
</tr>
<tr>
<td>CVR</td>
<td>5.1±0.081</td>
<td>2.17±0.10</td>
<td>1.24±0.10</td>
<td>1.24±0.10</td>
</tr>
<tr>
<td>Fast flow (ml/100 g/min)</td>
<td>69.8±10.11</td>
<td>176.3±21.0</td>
<td>59.9±4.70</td>
<td>55.5±8.03</td>
</tr>
<tr>
<td>Slow flow (ml/100 g/min)</td>
<td>18.5±3.14</td>
<td>15.6±5.04</td>
<td>16.3±2.04</td>
<td>24.6±1.10</td>
</tr>
<tr>
<td>Weight Fast (%)</td>
<td>53.6±5.07</td>
<td>50.4±2.06</td>
<td>49.4±4.87</td>
<td>53.6±5.07</td>
</tr>
<tr>
<td>Weight Slow (%)</td>
<td>46.4±2.22</td>
<td>49.3±2.14</td>
<td>49.6±2.14</td>
<td>50.6±1.42</td>
</tr>
<tr>
<td>Shed blood (ml/kg b.w.)</td>
<td>14.4±2.1</td>
<td>15.6±2.8</td>
<td>10.6±3.9</td>
<td>19.9±4.2</td>
</tr>
</tbody>
</table>

†Numbers represent the mean of 5 experiments ± SE.

Significant differences compared to control animals without premedication.

Premedication With 5 mg/kg PBZ

Hemodynamic Changes: (Table 2)

MABP was slightly increased during CO₂ inhalation. It was kept constant during Bl and B2, and it returned to the prebleeding level after transfusion (Control: 92.5; transf. 97.3 mm Hg).

Venous pressure measured in the sagittal sinus significantly increased during CO₂ inhalation. There was no significant change in the electrical activity of the brain (EEG) continuously deteriorated as hemorrhagic shock developed. There was electrical silence by the end of B2 and also after transfusion.
was also a significant difference between the 2 control (pre and post CO\textsubscript{2} inhalation) values: 15.0 and 6.8 mm Hg, respectively. Venous pressure slowly fell toward the end of B2 and rose to 10.6 mm Hg after retransfusion; this level was significantly higher than the second control value.

MCBF increased from 48.2 to 79.4 ml/100 g/min during CO\textsubscript{2} inhalation. The second control flow (flow \#3) was lower than flow \#1, i.e. 37.4 ml/100 g/min. MCBF increased toward the end of B1 and fell to the control level during B2. There was a significant increase of flow after retransfusion (56.9 ml/100 g/min). Regional blood flow values (an average of the mean flows of the probes overlying the frontal, parietal and temporo-occipital lobes) mirrored the variations in MCBF (fig. 1). The changes in fast (gray matter) and slow (white matter) flow compartments obtained by biexponential analysis of the washout curves closely followed those of the MCBF throughout the experiment, except that the slow flow did not increase significantly after retransfusion. The weights of both the fast and slow flows did not change significantly during the procedure.

Blood Gases (Table 3)

Arterial P\textsubscript{CO\textsubscript{2}} during flow 1 did not differ significantly from that of flow \#3 (43.2 ± 5.0 and 38.5 ± 3.2 mm Hg). However, the P\textsubscript{CO\textsubscript{2}} of flow \#3 was consistently lower than that of flow \#1. The CO\textsubscript{2} tension of the arterial blood rose to 71.0 mm Hg during CO\textsubscript{2} inhalation. During the remainder of the experiment there was no significant difference in P\textsubscript{CO\textsubscript{2}} as compared to the second control value.

Arterial P\textsubscript{O\textsubscript{2}} and O\textsubscript{2} saturation did not change significantly during the study. Venous O\textsubscript{2} saturation was 62.6% in the first control flow. It was 81.2% during CO\textsubscript{2} inhalation and 52.4% in the third flow. There was a further and significant decrease only in B2. Venous O\textsubscript{2} saturation exceeded the control value after retransfusion (69.7%).

Arterial and venous pH decreased significantly both in B2 and after retransfusion compared to control. The hemoglobin values fell significantly toward the end of hypovolemia.

Cerebral Metabolites

CMR\textsubscript{O\textsubscript{2}} was significantly higher in both B1 and B2 compared to the control and reached its highest level by the end of B2 (Control: 2.32 (Flow \#3); B2: 3.14 ml/100 g/min) (table 4).

The RQ usually exceeded 1 except during flow \#4 when it decreased to 0.93. RQ fell toward the end of hypovolemia (fig. 2).

Arterial lactate increased significantly during the study. A-V differences of lactate did not show significant differences throughout the experiment. CMR glucose was significantly less at the end of B2 compared to control (4.55 and 2.96 mg/100 g/min).

Electrocortico
gram

The electrocortico
gram did not show major changes either in B1 or in B2 after retransfusion compared to the control state.

Discussion

Reivich et al.\textsuperscript{11} have found MCBF to be 38 ± 3 ml/100 g/min at a P\textsubscript{CO\textsubscript{2}} level of 33 to 37 mm Hg in untreated baboons prior to bleeding. This value is identical to the present data. PBZ does not change MCBF though it significantly reduces arterial pressure. Similar observations were made by Hoff et al.\textsuperscript{16} and Sokoloff.\textsuperscript{17} However, Hashi et al.\textsuperscript{18} found a significant increase in CBF induced by PBZ. The difference in the results could be accounted for by the design of the 2 sets of experiments in that Hoff et al.\textsuperscript{16} measured CBF 2-4 hours after giving the drug whereas Hashi et al.\textsuperscript{18} measured during infusion.

PBZ does not change the sensitivity of CBF to changes in arterial P\textsubscript{CO\textsubscript{2}}. The alterations during CO\textsubscript{2} inhalation were of the same order as found by Nyary et al.\textsuperscript{9} in untreated animals. Hoff et al.\textsuperscript{16} showed that there was no significant effect of PBZ upon CBF during hypox- or normocapnia. The reactivity of the cerebral vessels to CO\textsubscript{2} may account for the differences observed between the control flows. Arterial P\textsubscript{CO\textsubscript{2}} was in every experiment higher during flow \#1 compared to flow \#3.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Flow #1</th>
<th>Flow #2</th>
<th>Flow #3</th>
<th>Flow #4</th>
<th>Flow #5</th>
<th>Flow #6</th>
<th>Flow #7</th>
<th>Flow #8</th>
<th>Flow #9</th>
<th>Retransfusion #10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Art. Pco₂ (mm Hg)</td>
<td>43.2</td>
<td>±4.99</td>
<td>38.5</td>
<td>36.7</td>
<td>38.7</td>
<td>34.0</td>
<td>40.9†</td>
<td>42.4†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ven. Pco₂ (mm Hg)</td>
<td>51.6</td>
<td>76.7</td>
<td>50.2</td>
<td>50.4</td>
<td>49.7</td>
<td>48.0</td>
<td>52.8</td>
<td>55.7</td>
<td>55.4</td>
<td>48.9</td>
</tr>
<tr>
<td>Art. Pco₂ (mm Hg)</td>
<td>110.5</td>
<td>115.8</td>
<td>105.6</td>
<td>105.0</td>
<td>107.5</td>
<td>101.0</td>
<td>110.2</td>
<td>108.5</td>
<td>109.9</td>
<td></td>
</tr>
<tr>
<td>Ven. Osat. (%)</td>
<td>72.6</td>
<td>76.7</td>
<td>50.2</td>
<td>50.4</td>
<td>49.7</td>
<td>48.0</td>
<td>52.8</td>
<td>55.7</td>
<td>55.4</td>
<td>48.9</td>
</tr>
<tr>
<td>Art. Osat. (%)</td>
<td>94.3</td>
<td>93.4</td>
<td>94.6</td>
<td>94.2</td>
<td>95.1</td>
<td>96.5</td>
<td>96.1</td>
<td>97.2</td>
<td>96.8</td>
<td>94.9</td>
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<tr>
<td>Art. pH</td>
<td>7.391</td>
<td>7.227</td>
<td>7.403</td>
<td>7.413</td>
<td>7.363†</td>
<td>7.348†</td>
<td>7.322†</td>
<td>7.294†</td>
<td>7.270†</td>
<td></td>
</tr>
<tr>
<td>Ven. pH</td>
<td>7.355</td>
<td>7.217</td>
<td>7.361</td>
<td>7.342</td>
<td>7.322†</td>
<td>7.388†</td>
<td>7.296†</td>
<td>7.241†</td>
<td>7.265†</td>
<td></td>
</tr>
<tr>
<td>Art. Hb (g/100 ml)</td>
<td>11.8</td>
<td>12.2</td>
<td>11.5</td>
<td>11.0</td>
<td>10.2</td>
<td>9.9</td>
<td>9.4</td>
<td>9.1</td>
<td>9.0</td>
<td>10.6</td>
</tr>
<tr>
<td>Ven. Hb (g/100 ml)</td>
<td>34.3</td>
<td>35.2</td>
<td>35.4</td>
<td>31.8</td>
<td>30.0</td>
<td>28.0</td>
<td>26.5</td>
<td>25.1</td>
<td>24.9</td>
<td>30.3</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>0.99</td>
<td>0.98</td>
<td>0.95</td>
<td>0.94</td>
<td>0.93</td>
<td>1.2</td>
<td>0.70</td>
<td>1.14</td>
<td>1.16</td>
<td>1.30</td>
</tr>
</tbody>
</table>

*Numbers represent the mean of 5 experiments ± SE.
†Significant differences compared to control animals without premedication.

**TABLE 4 Cerebral Metabolic Changes in the Phenoxybenzamine Pretreated Baboons**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Bleeding 1</th>
<th>Bleeding 2</th>
<th>Retransfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Art. glucose (mg/100 ml)</td>
<td>157.5±16.0</td>
<td>287.8±38.5</td>
<td>375.3±20.6</td>
<td>313.2±29.2</td>
</tr>
<tr>
<td>Ven. glucose (mg/100 ml)</td>
<td>145.8±15.1</td>
<td>267.1±38.9</td>
<td>369.7±22.2</td>
<td>305.0±31.7</td>
</tr>
<tr>
<td>Art. lactate (mM/l)</td>
<td>1.85±0.220</td>
<td>4.63±1.283</td>
<td>6.71±0.819</td>
<td>6.92±0.821</td>
</tr>
<tr>
<td>Ven. lactate (mM/l)</td>
<td>1.90±0.235</td>
<td>3.76±0.503</td>
<td>6.53±0.812</td>
<td>6.83±0.833</td>
</tr>
<tr>
<td>CMR glucose (mg/100 g/min)</td>
<td>4.55±0.85</td>
<td>4.50±1.30</td>
<td>2.96±0.62</td>
<td>5.55±0.27</td>
</tr>
<tr>
<td>CMR O₂ (ml/100 g/min)</td>
<td>2.32±0.18</td>
<td>2.91±0.38</td>
<td>3.14±0.18</td>
<td>2.98±0.65</td>
</tr>
<tr>
<td>RQ</td>
<td>1.64±0.51</td>
<td>1.43±0.90</td>
<td>1.20±0.20</td>
<td>1.37±0.28</td>
</tr>
</tbody>
</table>

*Numbers represent the mean of 5 experiments ± SE.
†Significant differences compared to control animals without premedication.

**FIGURE 2.** Cerebral metabolism of the baboon pretreated with 5 mg/kg phenoxybenzamine in hemorrhagic shock. CMR O₂ = cerebral metabolic rate of oxygen; CMR CO₂ = cerebral metabolic rate of CO₂; RQ = respiratory quotient; calculated CMR O₂ = amount of oxygen required for the complete metabolism of glucose consumed [1 mole of glucose requires 6 moles of oxygen].
MCBF increases by the end of B1 and is accompanied by a significant decrease in hemoglobin and hematocrit (table 3). Haggendal and Norback studied the effect of hemodilution upon CBF and found an exponential increase in flow when the hematocrit became less than 30%. MCBF does not fall below control levels in the PBZ pretreated animals during B2. This may be due, in part, to a vasodilatory effect of the drug. Fraser et al. reported that PBZ not only prevented the development of but also reduced the arterial spasm elicited by catecholamines in the cerebral vessels of monkeys. Increased sympathetic activity has been described in shock. This increased activity is reduced by PBZ. The sympatholytic effect of PBZ might also enhance the ability of the cerebral vasculature to autoregulate over a wider range of blood pressure, thus accounting for the preserved CBF during B2. Normally, the lowest pressure at which autoregulation of cerebral flow can be detected in hypotensive states is reported to be 50–60 mm Hg. Pretreatment with PBZ has been shown to extend the autoregulatory range down to approximately 30 mm Hg.

Halmagyi and Gillett showed that the systemic metabolic rate of untreated animals increased after retransfusion. In other studies, also performed without PBZ pretreatment, CBF improved after retransfusion.

As PBZ administration did not completely prevent acidosis from developing toward the end of shock, it is possible that the increase in MCBF is due to this change in pH. The developing acidosis is partly produced by the increase of blood lactate. Lacto-acidemia in shock is caused by excitation of the beta-receptors, which are not blocked by PBZ. However, cerebral venous lactate and pH changed in parallel with the arterial levels and CBF was not decreased during B2. This suggests that there is no change in cerebral lactic acid production and that PBZ has a beneficial effect on the microcirculation of the brain during shock.

Under normal conditions it is generally believed that the brain utilizes only glucose for its energy requirements. As a result, the RQ is close to unity. The present results suggest that PBZ may change the metabolic pathways of glucose. It can be seen from fig. 2 that CMRO₂ calculated from the glucose consumed by the brain, assuming aerobic metabolism, significantly exceeds the measured CMRO₂. RQ is also higher than 1 before bleeding. These metabolic changes are no longer present at the end of B2 when the 2 CMRO₂ values are similar and RQ is close to 1. Values after retransfusion tend to revert to the prebleeding ones. One possible explanation of these metabolic changes is that PBZ shifts normal cerebral metabolism from the utilization of glucose to other substrates before bleeding, and glucose consumption becomes the main metabolic pathway only during hemorrhage.

In conclusion, it was found that PBZ pretreatment prevented the fall in cerebral blood flow and CMRO₂ which occurs in systemic hypotension due to bleeding.

References

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Modification of Cerebrovascular CO$_2$ Reactivity by Inhibition of Dopamine $\beta$-Hydroxylase

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SUMMARY The influence of sympathetic nervous activity on cerebral circulation and cerebrovascular CO$_2$ reactivity was investigated through inhibition of dopamine $\beta$-hydroxylase (DBH). A Po$_2$ electrode, a PCO$_2$ electrode and a plate-type thermocouple-flowmeter were placed on the pial surface of the cat brain. Cerebrocortical Po$_2$, PCO$_2$, 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% CO$_2$ inhalation and hyperventilation were measured before and after the inhibition of DBH.

Following the intracarotid infusion of fusaric acid, cerebrocortical Po$_2$, and cerebrocortical blood flow increased significantly. After the inhibition of DBH, the degree of the increase in cerebrocortical Po$_2$ during 5% CO$_2$ inhalation was enhanced while the degree of the decrease in cerebrocortical Po$_2$ during hyperventilation did not show any significant change.

The cerebral vasodilatation caused by fusaric acid suggests that the sympathetic nervous system takes part in the resting tone of cerebral blood vessels. The increase in the cerebrovascular CO$_2$ reactivity produced by the inhibition of DBH suggests that the sympathetic nervous system modifies cerebrovascular CO$_2$ reactivity.

CEREBRAL BLOOD VESSELS have been found to be richly innervated with sympathetic nerve fibers, which appear to be most dense in the larger arteries. Dopamine $\beta$-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. In some conditions with an increased sympathetic discharge, 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 CO$_2$ 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-
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