Eicosapentaenoic Acid: Effect on Brain Prostaglandins, Cerebral Blood Flow and Edema in Ischemic Gerbils

K.L. Black, J.T. Hoff, N.S. Radin,* and G.D. Deshmukh*

SUMMARY Eicosapentaenoic acid prevents platelet aggregation and inhibits arachidonate conversion into thromboxane A$_2$ and prostaglandins. Consequently, eicosapentaenoic acid might protect the brain from the ischemia that follows cerebral arterial occlusion. We studied the effect of eicosapentaenoic acid on cerebral ischemia in anesthetized gerbils. Ischemia was produced by bilateral carotid occlusion for 10 min, followed by reperfusion for 60 min, in gerbils fed either a standard diet (control) or a diet supplemented with menhaden fish oil for 2 months. The menhaden fish oil contained 17 mole % eicosapentaenoic acid. Regional cerebral blood flow was measured by the hydrogen clearance method and brain water by the specific gravity technique. In control animals cerebral blood flow was decreased 30 and 60 min after reperfusion ($p < .001$) and brain water was increased ($p < .001$). In the experimental group cerebral blood flow did not fall during reperfusion and edema did not appear. Brain prostaglandins and thromboxane were measured by radiolmmunoassay. PGF$_{2\alpha}$, PGE$_2$, 6-keto PGF$_{1\alpha}$ and TXB$_2$ increased after severe ischemia and reperfusion. The synthesis of brain diene prostaglandins was not altered by eicosapentaenoic acid.

Our study indicates that eicosapentaenoic acid prevented post-ischemic cerebral edema and hypoperfusion, without affecting the levels of brain diene prostaglandin and thromboxane.

RECENTLY there has been increased interest in the role of arachidonic metabolites in cerebral ischemia and edema. Since prostaglandins, thromboxanes, and leukotrienes are not stored in mammalian tissues, it is generally thought that the rate-limiting step for their synthesis is the release of arachidonic acid from membrane phospholipids through the activation of phospholipase A$_2$. After bilateral carotid artery occlusion in gerbils the tissue content of free arachidonate is increased 20 to 40 times, but only small changes occur in the level of brain prostaglandins because depletion of tissue oxygen in severely ischemic brain limits arachidonic acid conversion to prostaglandin endoperoxides by cyclo-oxygenase, a step requiring molecular oxygen. However, during reperfusion of the brain after episodes of brief ischemia, there is a large accumulation of arachidonic acid metabolites in the brain. Presumably, re-establishment of blood flow restores tissue oxygen and permits the conversion of arachidonic acid to prostaglandins and leukotrienes. These products are potentially deleterious in ischemia. Inhibition of cyclo-oxygenase by indomethacin has been shown to prevent impaired cerebral flow (CBF) and brain edema after ischemia. The use of cyclo-oxygenase inhibitors such as indomethacin or aspirin in the treatment of cerebral ischemia is limited, however, because they also inhibit the production of prosta-cycalin (PGI$_2$) — a potent vasodilator and antiplatelet aggregator. In addition, indomethacin has little effect on leukotriene synthesis.

Eicosapentaenoic acid (EPA) is structurally similar to arachidonic acid (fig. 1). It competitively inhibits the oxidation of arachidonic acid by both cyclo-oxygenase and lipoxygenase. As with aspirin or indomethacin, EPA prevents prostaglandin and thromboxane formation in platelets. But unlike indomethacin, EPA is itself oxidized by cyclo-oxygenase to a prostacyclin (PGI$_2$). PGI$_2$ is an inhibitor of platelet aggregation.

The objective of the present investigation was to study the effects of an EPA-rich diet on CBF, brain water accumulation, free fatty acid levels, and brain prostaglandin synthesis after cerebral ischemia.

Materials and Methods

Animals and Diets

Eighty male mongolian gerbils (Meriones unguiculatus) weighing 31 to 63 g were the progeny of pregnant gerbils fed either a basal diet of Purina rat chow or the basal diet supplemented with 25% of the calories as menhaden fish oil (Zapata Haynie, Reedville, Virginia). Forty male gerbils from mothers fed the basal diet (control group) were continued on the basal diet for 2 months after weaning. Forty male gerbils from mothers fed the oil supplemented diet (experimental group) were continued on the supplemented diet for 2 months after weaning. The composition of menhaden fish oil, which contained 17 mole % EPA is presented in table 1.

Surgical Procedure

In all groups gerbils were anesthetized with ketamine 50 mg/kg and xylazine 20 mg/kg body weight injected intraperitoneally. A midline neck incision was made and the trachea was cannulated with a PE-90 polyethylene catheter. A PE-1 polyethylene catheter was inserted into the left femoral artery and connected to a blood pressure transducer. Blood samples (0.15 ml) were removed for blood gas measurements and hematocrit determinations. The removed blood volume was replaced with saline to avoid hypovolemia. Animals with abnormal blood pressures or arterial blood gases were discarded from the experiment. The

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Received March 15, 1983; revision accepted July 12, 1983.
right and left common carotid arteries were occluded with a Mayfield clip for 10 min. The clips were then removed to restore cerebral circulation. In sham animals the carotid arteries were exposed but not occluded. Ten control gerbils and 10 experimental gerbils had bilateral carotid occlusions for 10 min followed by 10 min of reperfusion. In less than 1 min the brains were then removed from anesthetized gerbils and placed in pentane, cooled in dry ice. Ten sham control and 10 sham experimental gerbils underwent the same procedure without carotid occlusion. The frozen brains were weighed and processed for brain analysis of prostaglandins and fatty acids.

Ten control gerbils and 10 experimental gerbils had brain specific gravity and CBF measurements. Four 125 μm diameter Teflon coated platinum iridium electrodes (with 0.5 mm of the Teflon coat removed from the tip) were inserted with micromanipulators into the grey matter of the animals through burr holes made on each side of the sagittal suture. Two were placed in front of the coronal suture and two behind; all were fixed in place with acrylic cement. A silver/silver chloride reference electrode was placed subcutaneously in the right leg. Measurements of CBF were taken prior to bilateral carotid occlusion, during occlusion, and 5 min, 30 min, and 60 min after reperfusion. Systemic blood pressure was monitored concurrently with each CBF measurement. After the last CBF measurement arterial blood gases were again measured. The animals were then killed and the brains were quickly removed and placed in kerosene for brain specific gravity determinations. The brains were similarly analyzed in 10 sham control and 10 sham experimental gerbils, without carotid occlusions or electrode placement.

**Measurements**

Regional CBF was evaluated by the hydrogen clearance technique. Brain specific gravity measurements were made as described by Nelson using a bromobenzene-kerosene density gradient column. Four samples of grey matter (2 mm³ surrounding each electrode, but excluding the area perforated by the electrode or white matter) were measured. The dissection was carried out under kerosene and samples were transferred immediately to the gradient column. Before each series of measurements droplets of known specific gravity were inserted to check the reliability of the column. A column was used only if the correlation coefficient of linearity was greater than 0.995.

PGE₂ was determined by radioimmunoassay using an antibody described by Fitzpatrick. The antibody (UpJohn) demonstrated high affinity to PGE₂ standard and ³H-PGE₂ (New England Nuclear) and low cross-reactivity to a number of related prostaglandins. Dextran-coated charcoal was used to separate bound from free ligand. The limit of sensitivity was 2.0 pg/tube. PGE₂ was determined also by a dextran-coated charcoal separation radioimmunoassay using an antibody described by Fitzpatrick. The limit of sensitivity was 1.3 pg/tube. 6-keto prostaglandin F₁α was determined by a radioimmunoassay kit (New England Nuclear). The separation of the antibody-antigen complexes from the free antigen was achieved by the adsorption of the free ³H tracer onto activated charcoal. The assay had low crossreactivity to the related prostaglandins. The limit of sensitivity was 4.5 pg/tube. Thromboxane B₂ was measured by a modified radioimmunoassay as reported by Fitzpatrick. Tritiated thromboxane B₂ (New England Nuclear) competes with "cold" thromboxane B₂ for available antibody sites on the thromboxane antisera. Free and antibody bound thromboxane B₂ were separated with dextran-coated charcoal.

**TABLE 1** The Total and Free Fatty Acid Composition of Gerbil Brains (mean ± SE) after Standard Diet (Control) and Eicosapentaenoate Rich Diet (Treated)

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Control</th>
<th>Treated</th>
<th>Control</th>
<th>Treated</th>
<th>Menhaden oil % mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:0</td>
<td>0.92 ± 0.62</td>
<td>0.79 ± 0.51</td>
<td>0.84 ± 0.94</td>
<td>1.02 ± 0.05</td>
<td>10.66</td>
</tr>
<tr>
<td>16:0</td>
<td>23.21 ± 0.67</td>
<td>23.51 ± 0.27</td>
<td>20.11 ± 1.04</td>
<td>20.90 ± 0.22</td>
<td>16.63</td>
</tr>
<tr>
<td>16:1</td>
<td>0.66 ± 0.08</td>
<td>0.87 ± 0.12</td>
<td>0.78 ± 0.15</td>
<td>1.09 ± 0.08</td>
<td>13.01</td>
</tr>
<tr>
<td>18:0</td>
<td>26.65 ± 0.98</td>
<td>26.46 ± 0.21</td>
<td>41.94 ± 1.34</td>
<td>44.01 ± 0.69</td>
<td>2.40</td>
</tr>
<tr>
<td>18:1 (n = 9)</td>
<td>20.55 ± 0.19</td>
<td>19.11 ± 0.57*</td>
<td>13.19 ± 0.16</td>
<td>10.75 ± 0.73*</td>
<td>11.12</td>
</tr>
<tr>
<td>18:2 (n = 6)</td>
<td>1.32 ± 0.01</td>
<td>0.76 ± 0.09*</td>
<td>1.49 ± 0.13</td>
<td>0.59 ± 0.05*</td>
<td>1.77</td>
</tr>
<tr>
<td>20:1 (n = 9)</td>
<td>1.44 ± 0.07</td>
<td>1.09 ± 0.21</td>
<td>0.59 ± 0.08</td>
<td>0.396 ± 0.41*</td>
<td>1.06</td>
</tr>
<tr>
<td>20:4 (n = 6)†</td>
<td>9.87 ± 0.17</td>
<td>9.10 ± 0.10*</td>
<td>17.46 ± 0.64</td>
<td>16.79 ± 0.38</td>
<td>1.84</td>
</tr>
<tr>
<td>20:5 (n = 3)††</td>
<td>0.00 ± 0.00</td>
<td>0.41 ± 0.07*</td>
<td>0.00 ± 0.00</td>
<td>1.12 ± 0.11*</td>
<td>17.04</td>
</tr>
<tr>
<td>22:6 (n = 3)</td>
<td>14.86 ± 1.23</td>
<td>17.53 ± 0.13*</td>
<td>3.47 ± 0.78</td>
<td>3.22 ± 1.64</td>
<td>7.96</td>
</tr>
</tbody>
</table>

*p < 0.02
†Arachidonate
‡Eicosapentaenoate
The sensitivity limit was 0.7 pg/tube. The cross-reactivity of antisera to triene prostaglandins (i.e., PGE₃, TXB₂, Δ⁷ 6-keto PGF₁α) has not been determined.

The composition of free and total fatty acids in brain were determined by gas liquid chromatography. Brain lipids were extracted with hexane/isopropanol and the free fatty acids were isolated by solvent partitioning. The acids were converted to methyl esters by treatment with methanol, concentrated HCl, and dimethoxypropane. For determination of the total brain fatty acids, the extracted lipids were heated overnight with methanolic HCl in a special methanolysis tube. In both cases, the methyl esters were purified by thin layer chromatography, then analyzed by gas liquid chromatography using a hydrogen flame detector and a column containing Silar 10C at 180 to 220 °C. Behenic acid was added to the free fatty acid fraction and the total lipids as internal standard.

Results

Figure 2 shows CBF (mean ± SE) in control and experimental gerbils. Regional CBF in the control group (n = 10), prior to carotid occlusion, was 21.0 ± 1.2 ml/100g/min (mean ± SE). During bilateral carotid artery occlusion CBF was less than 5 ml/100g/min. Five minutes after reperfusion a marked hypereflux was noted, flow increased to 42.1 ± 4.0 ml/100g/min in control gerbils and to 39.2 ± 3.1 ml/100g/min in experimental gerbils. In control gerbils CBF fell after 30 and 60 min of reperfusion to 16.8 ± 1.1 and 16.4 ± 1.2 ml/100g/min respectively (p < .001). In the experimental group reperfusion CBF's were not significantly lower than the pre-ischemic CBF. The initial flow was 18.9 ± 1.1 ml/100g/min. After ischemia and 30 and 60 min of reperfusion the flow was 17.7 ± 1.4 and 20.2 ± 1.4 ml/100g/min, respectively.

The data for brain specific gravity (fig. 3) show that there was a significant accumulation of brain water in control animals after severe ischemia and reperfusion. Brain specific gravity in control sham gerbils was 1.0494 ± 0.0001. In control gerbils after carotid occlusion and 60 min of reperfusion brain specific gravity decreased to 1.0481 ± 0.0003 (p < .001). In contrast, no significant change in brain water was noted in oil fed gerbils after ischemia. Brain specific gravity was 1.0487 ± 0.0003 and 1.0484 ± 0.0002 in sham and ischemic gerbils respectively. The difference in specific gravity between control ischemic and oil fed ischemic gerbils was not significant.

Brain prostaglandins and thromboxane were significantly increased after 10 minutes of ischemia and 10 minutes of reperfusion. PGF₂α, increased from 3.8 ± 1.0 to 38.0 ± 2.0 pg/mg brain in control gerbils, and from 4.2 ± 0.9 to 44.9 ± 5.8 pg/mg brain in oil fed gerbils. PGE₂ increased from 10.4 ± 4.0 to 16.6 ± 4.2 pg/mg brain in control, and from 15.4 ± 4.7 to 25.4 ± 5.8 pg/mg brain in experimental gerbils. 6-keto PGF₁α increased from 13.4 ± 4.2 to 28.4 ± 8.8 pg/mg brain in control and from 14.8 ± 6.4 to 26.2 ± 9.5 in experimental gerbils. TXB₂ increased from 2.2 ± 0.5 to 5.4 ± 1.0 pg/mg in control, and from 1.9 ± 0.5 to 4.7 ± 0.8 pg/mg brain in experimental gerbils. There was no significant difference in the synthesis of brain prostaglandins after ischemia and oil fed ischemic gerbils.

The composition of brain total and free fatty acids in control and treated groups is shown in table 1. Eight brains were pooled and considered as one sample. Gas liquid chromatography was performed on each sample twice. The mean, therefore, represents four values. EPA could not be detected in free or total fatty acids of control brain, but a significant level was seen in the oil fed animals: 0.41 % of the total acids and 1.12% of the total lipids as internal standard.

Body weight in menhaden oil supplemented gerbils was significantly lower than control gerbils, 40.7 ± 1.7 gms vs 54.9 ± 1.8 gms (mean ± SE) in treated and control gerbils respectively. Blood pressure, arterial blood gases and hematocrit were similar in both groups as shown in table 2. There was no mortality from bilateral carotid occlusion and reperfusion in either control or treated groups.

FIGURE 2. Cerebral blood flow (mean ± SE) in control and eicosapentaenoic acid fed gerbils prior to ischemia and after ischemia and reperfusion.

FIGURE 3. Brain specific gravity (mean ± SE) in control sham and ischemic gerbils and treated sham and ischemic gerbils.
Discussion

A therapeutic potential for EPA was suggested by the findings of Dyerberg\textsuperscript{25} who noted the high content of EPA in the maritime diet of Greenland Eskimos. EPA was suggested as an important factor in the low incidence of myocardial infarction in Eskimos.\textsuperscript{24-27} In a control group of Danes, platelet fatty acids contained 22% arachidonate, but EPA constituted only 0.5% of the platelet fatty acids. In contrast, Eskimo platelet fatty acids contained 8.5% arachidonate and 8% EPA. This accounted for an eicosapentaenoate/arachidonate ratio of 0.02 in Danes and 0.94 in Eskimos.\textsuperscript{28} Coagulation factors II, VII and X, prothrombin time, and activated partial thromboplastin time were the same in control group of Danes, platelet fatty acids contained 8.5% arachidonate and 8% EPA. This accounted for an eicosapentaenoate/arachidonate ratio of 0.02 in Danes and 0.94 in Eskimos.\textsuperscript{28} Coagulation factors II, VII and X, prothrombin time, and activated partial thromboplastin time were the same in Eskimos and Danes. However, platelets in 10 of 21 Eskimos tested did not aggregate in the presence of ADP or collagen.

Dyerberg\textsuperscript{25, 26} indicated that EPA acid could have an antiaggregatory action due to competitive inhibition of TXA\textsubscript{2} synthesis. This is in accord with the observation that EPA is bound to the enzyme cyclo-oxygenase from sheep vesicular gland with affinities (1.7 to 15 \textmu M) equal to or greater than the Km value for arachidonate. EPA is thus an effective competitive inhibitor.\textsuperscript{13, 26} Moncada and Vane,\textsuperscript{13} agreeing with this and citing evidence by Raz,\textsuperscript{30} have concluded that the use of EPA could afford a "dietary protection against thrombosis."\textsuperscript{13} Nevertheless, they regard the protective effect to be due to the possibility that eicosapentaenoic acid could be utilized by the vessel wall to make "an antiaggregating substance, probably a \Delta\textsuperscript{12} prostacyclin (PGI\textsubscript{12})" and an accompanying thrombox-

ane A\textsubscript{3} which is not a "proaggregatory agent." Morita,\textsuperscript{31} challenging this concept, could find neither conversion of EPA to \Delta\textsuperscript{12} 6-keto PGF\textsubscript{12}, by cultured murine aortic smooth muscle cells from rat aortas, nor to TXB\textsubscript{3} by rat platelets. Dyerberg,\textsuperscript{32} however, recently reported that human umbilical blood vessel walls transform EPA to PGI\textsubscript{3}. Dyerberg suggested that rat cyclo-oxygenase may have a greater specificity in its requirements of arachidonic acid than the human cyclo-oxygenase and that this could explain why experiments using rats have failed to demonstrate any conversion of EPA to PGI\textsubscript{3}.

Although EPA is reported to inhibit platelet prostaglandin synthesis,\textsuperscript{14} brain prostaglandin synthesis was not inhibited in our study. Needleman\textsuperscript{33} has emphasized that an EPA/arachidonate ratio close to 1.0 may be necessary for EPA to significantly inhibit prostaglandin formation. Brain enzymes may discriminate against EPA in lipid synthesis and brain lipids have a much slower turnover rate than platelet lipids. In this study the ratio of EPA/arachidonate in brain lipids only changed from 0.07 to 0.10. In contrast, this ratio in the platelet lipids of menhaden oil supplemented dogs was changed from 0.06 to 1.46 and similar changes in platelet lipids have been reported in man.\textsuperscript{35} Since EPA is incorporated to a much greater extent in platelets, the failure to inhibit brain prostaglandins does not rule out the possibility that platelet prostaglandins and thromboxane are inhibited by EPA rich diets. Moreover, triene prostaglandins were not measured. Whether the vessel wall synthesized PGI\textsubscript{3} from EPA, preventing platelet aggregation and promoting reperfusion, cannot be excluded by this study.

The conclusion by Iannotti\textsuperscript{11} that prostaglandins are involved in the development of cerebral edema gives impetus to understanding the manner in which EPA could influence brain water accumulation. Inhibition of cyclo-oxygenase was shown to reduce edema formation at low cerebral blood flows. Alternatively, EPA could compete with arachidonate for binding sites on lipoxigenase,\textsuperscript{12} reducing leukotriene synthesis. Leukotrienes (LTC\textsubscript{4}, LTD\textsubscript{4}, and LTE\textsubscript{4}) increase vascular permeability\textsuperscript{26} which could result in increased brain water accumulation during ischemia. Leukotrienes may also directly contribute to tissue damage by releasing enzymes such as lysozyme.

Why brain specific gravity is lower in sham gerbils on the oil supplemented diet is difficult to explain. We did not find an increase in the ratio of brain lipids to nonlipids in gerbils on the oil supplemented diet. Most likely the lower specific gravity represents an increase in water accumulation in sham experimental gerbils. Polyunsaturated fatty acids have been shown to produce edema in cortical slices.\textsuperscript{37, 38} The high content of polyunsaturated fatty acids in the oil diet may therefore

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**Table 2** Blood Pressure, Arterial Blood Gases and Hematocrit in Control and Treated Gerbils during Cerebral Ischemia and Reperfusion

<table>
<thead>
<tr>
<th></th>
<th>BP (mm Hg)</th>
<th>PaCO\textsubscript{2}</th>
<th>PaO\textsubscript{2}</th>
<th>pH</th>
<th>HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>60.3 ± 3.8</td>
<td>38.0 ± 1.8</td>
<td>110.0 ± 4.2</td>
<td>7.25 ± 0.018</td>
<td>38.9 ± 1.7</td>
</tr>
<tr>
<td>Treated</td>
<td>57.0 ± 2.4</td>
<td>39.2 ± 1.1</td>
<td>94.8 ± 7.5</td>
<td>7.24 ± 0.022</td>
<td>40 1 ± 1.3</td>
</tr>
</tbody>
</table>
account for the lower specific gravity in sham oil fed gerbils.

Two important points regarding this study require mention. First, menhaden fish oil and not pure EPA was used to supplement the experimental diet. Although EPA is the major constituent (table 1), menhaden oil may contain other components which could account for a beneficial or deleterious effect. Second, the weight gain was significantly less in experimental gerbils during the 2 months of diet supplementation, despite both control and oil fed groups being fed ad lib. The difference in weight gain could be explained either by a toxic effect of the oil diet or to a lower caloric intake by gerbils on the supplemented diet. Clearly future experiments using a diet supplemented with pure EPA and with control and experimental groups pair-fed to prevent weight differences are warranted.

Our study has shown that EPA rich diets prevent post-ischemic hypoperfusion and reduce brain edema after temporary arterial occlusion. Pretreatment with EPA may be therapeutically more useful in antiplatelet therapy than aspirin or indomethacin because of reduced leukotriene and platelet thromboxane formation and increased PGI₂ synthesis. The toxic effects of EPA are, however, not entirely known and human studies should, therefore, be deferred.

Acknowledgment

Financial support was from a NIH Biomedical Research Support Grant and NS 17760-04.

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Eicosapentaenoic acid: effect on brain prostaglandins, cerebral blood flow and edema in ischemic gerbils.

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Stroke. 1984;15:65-69
doi: 10.1161/01.STR.15.1.65

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