Blood–Brain Barrier Sodium Transport Limits Development of Brain Edema During Partial Ischemia in Gerbils

A. Lorris Betz, MD, PhD, Steven R. Ennis, PhD, and Gerald P. Schielke, MS

Sodium derived from the blood is known to accumulate in brain tissue during the early stages of incomplete ischemia. Our present studies were undertaken to determine the relation between blood–brain barrier sodium transport and the development of ischemic brain edema. Incomplete cerebral ischemia was produced in gerbils by ligation of the left common carotid artery under ether anesthesia. Following recovery from the anesthetic, the gerbils were evaluated for the presence of neurologic symptoms and were divided into symptomatic (n=77) and asymptomatic (n=94) groups. Tissue water, sodium, and potassium contents, tissue plasma volume, and brain uptake of 22Na were measured in both groups 1.5, 3, 6, 12, and 24 hours after carotid ligation. There was a progressive accumulation of sodium and water in the ipsilateral cerebral cortex of the symptomatic group compared with either the corresponding contralateral cortex of the same gerbils or with the asymptomatic group. Net changes in brain sodium and potassium concentrations appeared to be the main determinants of fluid accumulation. Brain edema was not due to opening of the blood–brain barrier because the unidirectional transport of 22Na remained low and was even reduced by 35–55% in the ischemic cortex. Nevertheless, this sodium transport activity appeared to be rate-limiting in the development of brain edema during the first 3 hours of ischemia because the rate of sodium accumulation in the tissue was the same as the rate of 22Na transport from the blood to the brain. We conclude that blood–brain barrier sodium transport is an important factor in the formation of ischemic brain edema. (Stroke 1989;20:1253–1259)

Brain edema is an inevitable consequence of cerebral ischemia, and edema contributes significantly to the morbidity and mortality associated with a stroke. Despite its frequent occurrence, there are currently no specific therapies to prevent or slow the development of ischemic edema. While its complete elimination might occur only with prompt restoration of energy metabolism, edema accumulation may be slowed in the face of continued ischemia by blocking the rate-limiting step in edema development.

Early after a stroke, brain edema occurs as a result of the accumulation of osmotically active molecules within brain cells.1 The brain contents of sodium2–7 or other osmoles2–7,8 have been correlated with the appearance of edema. Whether the accumulation of these substances is rate-limiting for the development of edema has not been determined. We investigated the role of sodium in the development of edema during the first 24 hours of incomplete cerebral ischemia in gerbils. Since the sodium that accumulates in the brain under these conditions is derived from the blood, we compared the rate of change of brain sodium content with the rate of sodium transport across the blood–brain barrier (BBB). Some of our results have been presented in a preliminary communication.9

Materials and Methods

Incomplete cerebral ischemia was produced by occlusion of the left common carotid artery in gerbils (Meriones unguiculatus). Males weighing 50–115 g were anesthetized with ether; the left common carotid artery was exposed, ligated in two places with 6-0 silk suture, and electrocauterized. After closure of the neck incision, the gerbils were allowed to recover from the anesthesia. Previous studies have shown that gerbils with severe neurologic symptoms following unilateral carotid artery


Supported by National Institutes of Health Grant NS-23870 and by a grant-in-aid from the American Heart Association through funds contributed in part by the Michigan Affiliate.

Address for reprints: A. Lorris Betz, MD, PhD, D3227 Medical Professional Building, University of Michigan, Ann Arbor, MI 48109-0718.

Received January 25, 1989; accepted March 9, 1989.
occlusion have a moderately severe level of ischemia, while gerbils with little or no neurologic symptoms lack significant ischemia. 10, 11 Therefore, 30 minutes after carotid ligation we used the neurologic evaluation scale developed by Ohno et al 11 to select two groups of gerbils; we included those with a stroke index of ≥10 in the symptomatic group and those with a stroke index of ≤3 in the asymptomatic (control) group. We excluded gerbils with intermediate levels of ischemia (stroke index between 3 and 10).

Approximately 1 hour before termination of the experiment, the gerbils were anesthetized with 50 mg/kg i.p. sodium pentobarbital and the femoral blood vessels were catheterized for monitoring blood pressure, for sampling arterial blood, and for the intravenous injection of isotopes. We eliminated three gerbils with blood pressure of <60 mm Hg, PO2 of <60 mm Hg, or PCO2 of >60 mm Hg. Experiments were terminated at the designated time by decapitating the gerbils, and 1-mm3 samples were punched with a biopsy needle from the parietal cortex of the right and left hemispheres of all gerbils for the determination of specific gravity. 12 The blood vessels were catheterized for monitoring blood pressure, for sampling arterial blood, and for the intravenous injection of isotopes. We eliminated three gerbils with blood pressure of <60 mm Hg, PO2 of <60 mm Hg, or PCO2 of >60 mm Hg. Experiments were terminated at the designated time by decapitating the gerbils, and 1-mm3 samples were punched with a biopsy needle from the parietal cortex of the right and left hemispheres of all gerbils for the determination of specific gravity. 12 The remaining right and left cortices were quickly separated, cleaned of external blood, weighed, and prepared for the appropriate assay.

Brain water content was determined from wet and dry weights; sodium and potassium contents were determined by flame photometry 5 in 25 symptomatic and 29 asymptomatic gerbils. Blood volume and plasma volume (PV) were determined from the brain and blood contents of chromium-51-labeled erythrocytes and iodine-125-labeled bovine serum albumin 2 minutes after intravenous injection of a mixture of these isotopes 5 in 24 symptomatic and 27 asymptomatic gerbils.

BBB permeability to sodium was determined in 28 symptomatic and 38 asymptomatic gerbils by a modification of the method described previously. 5 An intravenous bolus injection of saline containing 8 μCi of 22Na was allowed to circulate for 10 minutes before the rat was decapitated and the tissue and plasma contents of 22Na were determined. In most studies of this type, BBB permeability (PS product) is determined at a single time from the extravascular radioactivity (Cev) divided by the integral of the arterial blood radioactivity (C a) over the time of the experiment. 13

\[
P_S = C_{ev}/\int C_a dt \quad (1)
\]

Cev in the brain is estimated by subtracting the intravascular radioactivity from the total radioactivity (Cev) using the average PV obtained in a separate group of animals and the final plasma radioactivity (Cp).

\[
C_{ev}^{est} = C_{br} - PV \times C_p \quad (2)
\]

While this method can be used to determine BBB permeability in a few animals, it overestimates true BBB permeability since low-molecular-weight radiotracers initially distribute in a brain space that is greater than PV. 14, 15 This so-called rapidly filling space (RFS) can be measured by a graphical analysis method in which Cbr is determined at several times following the intravenous injection of an isotope. 15, 16 With this method, Cbr is plotted as a function of the integral over time of C a. The y intercept is then equal to RFS, and the slope is the true BBB permeability expressed as the product of the tracer's permeability and the surface area of the perfused capillary bed (PS product). If RFS is known, then true BBB permeability can be accurately quantified using a single-time experiment. Therefore, to obtain a more accurate estimate of BBB permeability to sodium from our 10-minute, single-time experiments, we determined RFS of ischemic and nonischemic cortex after 3 hours of unilateral carotid artery occlusion in 17 other symptomatic gerbils. Cbr and the integral of C a over time were measured after 5 minutes in four, after 10 minutes in seven, and after 20 minutes in six gerbils.

Figure 1 shows the plot of Cbr for 22Na, corrected for PV and normalized for Cpr vs. Cbr for 22Na integrated over the time of the experiment and also normalized for Cpr. Least-squares regression analysis for the contralateral (nonischemic) cortex yielded a mean±SEM y intercept (RFS) of 14.8±3.6 μl/g and a mean±SEM slope (PS product) of 2.30±0.18

FIGURE 1. Graph of determination of blood-brain barrier permeability (PS product) and size of rapidly filling space for 22Na in cerebral cortex of 17 gerbils subjected to unilateral carotid occlusion for 3 hours and then given intravenous injection of 22Na. Isotope concentration in blood was continuously monitored to integrate its concentration over time \((fC_a dt)\). Experiments were terminated after 5, 10, or 20 minutes, and final plasma isotope concentration \((C_p)\) and extravascular \(22Na (C_{ev})\) in ischemic (•) and nonischemic (○) cortices were determined. Slope of line is equal to PS product for \(22Na\). y intercept represents rapidly filling space that is not protected by blood–brain barrier and that is distinct from plasma space for albumin.
TABLE 1. Characteristics of Gerbil Groups After Unilateral Carotid Occlusion

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Asymptomatic</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5</td>
<td>3</td>
<td>6</td>
<td>12</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Stroke index</td>
<td>0.7±0.3</td>
<td>0.7±0.3</td>
<td>0.7±0.2</td>
<td>0.6±0.2</td>
<td>0.5±0.2</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>73.8±92.2</td>
<td>76.7±2.7</td>
<td>71.0±1.9</td>
<td>73.2±2.4</td>
<td>77.7±1.9</td>
<td></td>
</tr>
<tr>
<td>Temperature (° C)</td>
<td>37.2±0.2</td>
<td>37.4±0.1</td>
<td>38.1±0.2</td>
<td>37.7±0.1</td>
<td>37.9±0.2</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.36±0.01</td>
<td>7.38±0.01</td>
<td>7.40±0.01</td>
<td>7.36±0.01</td>
<td>7.37±0.01</td>
<td></td>
</tr>
<tr>
<td>PCO2 (mm Hg)</td>
<td>46.8±1.4</td>
<td>41.7±1.2</td>
<td>40.2±0.9</td>
<td>42.4±1.2</td>
<td>42.4±1.1</td>
<td></td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
<td>76.0±2.5</td>
<td>75.8±2.3</td>
<td>70.3±1.6</td>
<td>71.9±1.7</td>
<td>78.0±2.3</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.387±0.009</td>
<td>0.376±0.010</td>
<td>0.356±0.012</td>
<td>0.366±0.009</td>
<td>0.383±0.007</td>
<td></td>
</tr>
<tr>
<td>Specific gravity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral cortex</td>
<td>1.0478±0.0003</td>
<td>1.0479±0.0003</td>
<td>1.0472±0.0005</td>
<td>1.0467±0.0005</td>
<td>1.0453±0.0007</td>
<td></td>
</tr>
<tr>
<td>Contralateral cortex</td>
<td>1.0485±0.0003</td>
<td>1.0477±0.0005</td>
<td>1.0480±0.0004</td>
<td>1.0484±0.0003</td>
<td>1.0470±0.0005</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Symptomatic</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18</td>
<td>17</td>
<td>13</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Stroke index</td>
<td>13.2±0.4*</td>
<td>13.3±0.4*</td>
<td>12.4±0.3*</td>
<td>12.2±0.5*</td>
<td>12.2±0.7*</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>74.5±2.3</td>
<td>77.2±2.4</td>
<td>74.2±2.8</td>
<td>73.0±2.7</td>
<td>74.5±3.2</td>
<td></td>
</tr>
<tr>
<td>Temperature (° C)</td>
<td>37.2±0.2</td>
<td>37.6±0.2</td>
<td>37.5±0.2</td>
<td>37.6±0.2</td>
<td>38.3±0.3</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.36±0.01</td>
<td>7.38±0.01</td>
<td>7.39±0.04</td>
<td>7.33±0.02</td>
<td>7.38±0.02</td>
<td></td>
</tr>
<tr>
<td>PCO2 (mm Hg)</td>
<td>45.2±1.0</td>
<td>39.5±1.0</td>
<td>40.7±1.5</td>
<td>39.7±1.4</td>
<td>36.1±2.0</td>
<td></td>
</tr>
<tr>
<td>Po2 (mm Hg)</td>
<td>76.4±1.9</td>
<td>77.9±1.9</td>
<td>78.3±2.5</td>
<td>82.5±2.6</td>
<td>80.8±3.4</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.403±0.008</td>
<td>0.372±0.008</td>
<td>0.357±0.020</td>
<td>0.377±0.009</td>
<td>0.380±0.012</td>
<td></td>
</tr>
<tr>
<td>Specific gravity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Ipsilateral cortex                  | 1.0458±0.0003*| 1.0447±0.0003*| 1.0420±0.0007*| 1.0403±0.0008*| 1.0361±0.0015*|*
| Contralateral cortex                | 1.0488±0.0005| 1.0487±0.0005| 1.0478±0.0006| 1.0480±0.0006| 1.0477±0.0008|*

Data are mean±SEM. *p<0.001, 0.01, respectively, different from asymptomatic by Student’s two-tailed unpaired t test.

It should be noted that, as we define RFS, it is distinct from PV. If Cbr uncorrected for PV is used in the graphical analysis, then the y intercept is the sum of PV and RFS. If we determined PV separately, RFS was determined after correction for PV. Consequently, our calculated RFS was used in the calculation of Cev for 22Na according to the following modification of Equation 2:

\[
C_{ev} = C_{br} - C_{p}(PV + RFS)
\]

In the experiments we report here, PS product was calculated using a 10-minute uptake period and Equations 3 and 1.

Data are expressed as mean±SEM. Results from the groups were compared using Student’s two-tailed t test for unpaired data. Within a group, results from the corresponding ipsilateral and contralateral cortexes in the same gerbil were compared using Student’s t test for paired samples. A probability value of <0.05 was considered to indicate significance.

22Na, 51Cr (sodium chromate), and Protosol were purchased from DuPont-New England Nuclear (Boston, Massachusetts). [125I]Albumin (bovine serum) was obtained from ICN Radiochemicals (Irvine, California). All other chemicals were obtained from Sigma Chemical Co. (St. Louis, Missouri).

Results

Values for the stroke index, physiologic parameters, and cortical specific gravities are shown in Table 1. Since it was used as the basis for grouping the gerbils, there was, as expected, a large difference in stroke index between groups.

In the asymptomatic gerbils, there were no significant differences between specific gravities of the ipsilateral and contralateral cortexes at any time. Likewise, specific gravity of the contralateral cortex in the symptomatic group did not differ significantly from that in the contralateral cortex in the asymptomatic group. However, specific gravity of the ipsilateral cortex in symptomatic gerbils was significantly lower than that of either the corresponding contralateral cortex or of the ipsilateral cortex in the asymptomatic group. Furthermore, specific gravity of the ipsilateral cortex in symptomatic gerbils progressively decreased with increasing duration of ischemia, indicating a time-dependent accumulation of brain edema.

There were small but significant differences between groups in Po2 after 6 and 12 hours of...
ischemia and in PCO₂ after 24 hours. Since PO₂ was higher in the symptomatic than in the asymptomatic group, these differences were not believed to have significantly affected the results of our study.

Brain water and sodium contents increased and potassium content decreased progressively with increasing duration of ischemia in the ipsilateral cortex of the symptomatic group (Figure 2). In contrast, values for the contralateral cortex of the symptomatic group, and for both cortices of the asymptomatic group, remained relatively constant. While the concentrations of sodium and potassium changed reciprocally, the increase in sodium exceeded the decrease in potassium at every time.

Thus, there was an overall increase in the concentration of these major brain cations.

Net changes in brain water, sodium, and potassium contents in the symptomatic gerbils were calculated by subtracting contralateral from corresponding ipsilateral values; the net change in brain cation concentration was then determined by adding the changes in sodium and potassium contents. As shown in Figure 3, there was a nearly linear increase in total brain cation content over the 24 hours of ischemia. The net change in water content also increased progressively but at a greater rate during the first 3 hours than during later times. The relative importance of the net change in cation concentration to the observed change in brain water content was determined by assuming that the increase in cation content would be accompanied by an isosmotic influx of water. As shown in Figure 3, the change in brain cation concentration could account for all of the observed edema accumulation at 1.5, 12, and 24 hours of ischemia. At 3 and 6
TABLE 2. Plasma Volume of Cerebral Cortex of Gerbils After Unilateral Carotid Occlusion

<table>
<thead>
<tr>
<th>Cortex</th>
<th>1.5</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>6.60±0.17</td>
<td>7.20±0.57</td>
<td>6.59±0.24</td>
<td>6.47±0.65</td>
<td>6.78±0.28</td>
</tr>
<tr>
<td>Contralateral</td>
<td>6.88±0.53</td>
<td>7.30±0.58</td>
<td>6.50±0.25</td>
<td>6.34±0.60</td>
<td>6.42±0.31</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>5.08±0.40*†</td>
<td>6.66±0.73</td>
<td>5.95±0.13†</td>
<td>5.71±0.45</td>
<td>5.92±0.60</td>
</tr>
<tr>
<td>Contralateral</td>
<td>5.74±0.33</td>
<td>6.19±0.46</td>
<td>6.52±0.54</td>
<td>5.59±0.29</td>
<td>5.84±0.47</td>
</tr>
</tbody>
</table>

Values are mean±SEM µg/g wet wt.
* p<0.01 different from asymptomatic by Student’s two-tailed unpaired t test.
† p<0.05 different from corresponding contralateral cortex in same gerbil by Student’s two-tailed paired t test.

hours, the change in cation concentration accounted for 75% of the edema; however, differences between the observed and calculated changes in water content were not significant even at these times.

PV of the ipsilateral compared with the corresponding contralateral cortex was significantly reduced by 11% and 9% at 1.5 and 6 hours, respectively, in the symptomatic gerbils (Table 2). Differences between groups were significant only at 1.5 hours.

PS product for sodium in the ipsilateral cortex of the symptomatic gerbils decreased by 35–55% at all times compared with that in the corresponding contralateral cortex (Figure 4). Values from the contralateral cortex of the symptomatic group did not differ from those observed in the asymptomatic group. Thus, the decrease in the rate of unidirectional sodium transport from the blood to the brain persists over 24 hours. Furthermore, since there was no marked increase in sodium PS product with time, it does not appear that the BBB breaks down before 24 hours in this model of continuous partial ischemia.

Finally, PS product for sodium transport across the BBB was compared with the rate at which total brain sodium content increased during ischemia. For this comparison, it was first necessary to express the data for sodium content and sodium transport in the same units. Thus, the data for brain sodium content (Figure 2) were expressed in terms of wet weight. PS product, on the other hand, was converted to a rate of sodium flux by multiplying it by the average serum sodium concentration (157 meq/l). Total brain sodium changed more rapidly during the initial period of ischemia than it did later (Figure 5). During the first 3 hours of ischemia, the rate of change of total brain sodium content was 0.169±0.024 µeq/g wet/min (n=14). For comparison,
the rate of unidirectional flux of isotopic sodium was 0.195±0.026 μeq/g wet/min (n=14) for 1.5 and 3 hours and 0.214±0.020 μeq/g wet/min (n=28) over the entire 24 hours. These results suggest that, during the first 3 hours of ischemia, the rate of increase in brain sodium is limited by the rate at which sodium crosses the BBB. Since the development of brain edema is closely related to the increase in brain sodium content, we conclude that BBB sodium transport is rate-limiting for the formation of early ischemic brain edema.

**Discussion**

Ischemic brain edema follows a progressive course, in part because different mechanisms of edema formation are involved at different times following the occlusion of a major cerebral vessel. During the first hours of ischemia, the brain swells as a result of the accumulation of small, osmotically active molecules in the brain cells. Since the water accumulates primarily within cells and the BBB remains intact, this type of edema has been called cytotoxic or intact-barrier edema. If the partial BBB to water is high and is limited primarily by the development of brain edema, associated with an influx of plasma proteins, is seen. This type is known as vasogenic open-barrier edema. However, these sequential mechanisms for edema formation do not entirely explain the progressive nature of edema accumulation since edema appears gradually throughout the intact-barrier phase. Thus, other factors must be responsible for regulating the rate at which ischemic edema forms. Understanding these factors could eventually lead to interventions directed at slowing the rate of edema accumulation.

Blood is the primary source of edema fluid and, therefore, the rate of movement of water from the blood to the brain could control the rate of edema development. Normally, the permeability of the BBB to water is high and is limited primarily by the rate at which blood flows into the tissue. If cerebral blood flow drops to very low levels, for example, to <7 mL/100 g/min in gerbils, the accumulation of edema fluid is limited by the rate at which water is supplied by the blood. At higher blood flow rates, however, the amount of edema increases as cerebral blood flow decreases. Thus, something other than cerebral blood flow determines the extent to which the brain swells during moderate levels of ischemia.

With the BBB intact, the driving force for fluid movement into the ischemic tissue is provided by the accumulation of small molecules such as sodium and lactate. In many studies, the rate of edema accumulation is closely related to the rate at which tissue sodium content increases. In some studies, however, significant edema occurred even before brain cation concentrations had changed. Our results suggest that brain edema formation is closely related to changes in sodium and potassium contents, although during the first 6 hours of ischemia a small portion of the edema may have been caused by the generation of other tissue osmoles, such as lactic acid. Therefore, it may be possible to control the rate of edema development by controlling the rate at which brain cation concentrations change.

Despite the low permeability of the BBB to sodium, specific carrier-mediated transport processes are believed responsible for moving sodium from the blood to the brain. These carrier-mediated processes include Na,K-ATPase, sodium-hydrogen exchange, and sodium–chloride cotransport systems. In normal brain, the continuous influx of sodium via these carrier-mediated processes must be balanced, in part, by a flow of fluid through the brain’s interstitial spaces and by the efflux of sodium from the brain back into the blood. As a result, there is no net change in brain water or sodium content. Since Na,K-ATPase in the capillaries provides the driving force for BBB sodium transport and the secretion of interstitial fluid, there is also the possibility for sodium uptake in exchange for potassium efflux. If this exchange process is tightly coupled, then three sodium ions would be exchanged for every two potassium ions, thereby providing a mechanism for the long-term regulation of potassium concentration in the brain’s interstitial fluid.

Our findings are quite consistent with this model of BBB sodium transport. For example, the reduction in sodium PS product in ischemic brain may be due either to a reduction in permeability because of the failure of capillary Na,K-ATPase or, more likely, to a reduction in surface area due to incomplete perfusion of the vascular bed (unpublished results). Furthermore, the increase in brain sodium content seen during ischemia was accompanied by a simultaneous decrease in potassium concentration. The ratio of the change in sodium content to that in potassium was 1.92±0.24 (n=5) after 1.5 hours, 1.67±0.08 (n=5) after 3 hours, 1.65±0.22 (n=4) after 6 hours, and 1.70±0.08 (n=6) after 12 hours of ischemia; none of these values is significantly different from the theoretical value of 1.5 that would result from a three-for-two exchange of sodium for potassium. Finally, the rate of change of brain water content during the first 3 hours of ischemia was 0.13±0.02 μL/g wet/min (n=14), which is quite similar to the interstitial fluid production rate of 0.11–0.29 μL/g wet/min reported for normal rat brain. In ischemic brain, however, the interstitial fluid that is secreted by the capillaries does not flow away from its site of secretion as it does in normal brain. Instead, the fluid remains in the tissue, possibly because cellular ionic gradients have dissipated, which results in a large brain space with a sodium concentration lower than that of the surrounding nonischemic brain and cerebrospinal fluid. Alternatively, reduction in the size of the extracellular space may reduce the flow of fluid secreted by the capillaries until tissue pressure...
increases sufficiently to overcome the increased resistance to flow.

Our model assumes that brain capillary endothelial cells are less affected by the energy failure that accompanies partial ischemia than are other brain cells. Since endothelial cells are in direct contact with the oxygen provided by any residual blood flow, we believe that this selective preservation of active transport by brain capillaries is a good possibility. Furthermore, endothelial cells may be able to use glycolytic metabolism longer than other cells in the brain because their closer proximity to blood could give them preferential access to glucose and may make it easier for the endothelium to dispose of lactic acid.

For at least the first 3 hours of ischemia, BBB sodium transport appears to be the rate-limiting step in cation-dependent edema fluid accumulation. This suggests that edema might form at a greater rate if blood-to-brain sodium flux were increased by opening the BBB. We did not observe a breakdown of the BBB at any time during the 24 hours of our study. It is important to note, however, that mortality in the group of symptomatic gerbils increased from 28% at 12 hours to 46% at 24 hours. It is possible that BBB breakdown leads to a progression of edema and death that was too rapid to be seen among the surviving gerbils we used.

Our results have important implications for therapy of ischemic brain edema. Since edema formation is limited by BBB transport of sodium, drugs that inhibit sodium transport in brain capillaries may delay the accumulation of brain edema during ischemia. The combination of this type of agent with others designed to reduce ischemic neuronal damage might significantly reduce the morbidity and mortality associated with stroke.

Acknowledgments
The authors thank Mary Beer for her excellent technical assistance and Gloria Rodriguez for her valuable secretarial support.

References

Key Words: • blood–brain barrier • brain edema • gerbils
Blood-brain barrier sodium transport limits development of brain edema during partial ischemia in gerbils.
A L Betz, S R Ennis and G P Schielke

*Stroke.* 1989;20:1253-1259
doi: 10.1161/01.STR.20.9.1253

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/20/9/1253

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/