Brain edema is an important clinical complication of cerebral ischemia; however, there are no effective clinical measures to limit its development. This may be due, in part, to an incomplete understanding of the factors that lead to the production of ischemic brain edema. Numerous studies have shown that, in the first several hours following a stroke, brain edema is principally of the cytotoxic type. The blood–brain barrier (BBB) remains intact, and fluid accumulates in response to an increase in tissue osmoles. While a portion of the increase in tissue osmoles is due to breakdown of cellular constituents, there is also a good correlation between ischemic stroke, brain edema is principally of the cytotoxic type. The blood–brain barrier (BBB) remains intact, and fluid accumulates in response to an increase in tissue osmoles. While a portion of the increase in tissue osmoles is due to breakdown of cellular constituents, there is also a good correlation between ischemic edema and increases in brain sodium. Since the increased sodium content is seen only during incomplete and not during total ischemia, the source of sodium must be the blood. Therefore, some investigators have proposed that during incomplete ischemia, the rate of sodium influx from blood to brain is increased as the result of either diffusion down a concentration gradient or stimulation of specific sodium transport systems in the BBB. To date there have been no direct measurements of the rate of sodium uptake into ischemic brain tissue.

In this study, we measured BBB permeability to sodium and sucrose in a model of unilateral cerebral ischemia to test the hypothesis that enhanced uptake of sodium by brain tissue contributes to the formation of ischemic brain edema. Preliminary reports of some of these results have been presented.

Materials and Methods

Experiments were conducted using Mongolian gerbils (Meriones unguiculatus) that exhibited neurologic symptoms after occlusion of one common carotid artery. Male retired breeders weighing 75–105 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 animals were allowed to recover from the anesthesia. Thirty minutes after ligation, the gerbils were observed for neurologic symptoms, including circling, hemiparesis, seizures, and/or obtundation. Nonsymptomatic animals were excluded from the study.

At 2 hours after carotid ligation, the gerbils were anesthetized with sodium pentobarbital (50 mg/kg i.p.,) and the femoral blood vessels were catheterized. In all experiments, the right femoral artery was used to monitor the arterial blood pressure and to obtain a sample for blood gas determination. Radioactive tracers were injected through the left femoral vein. In addition, the left femoral artery was catheterized in the blood flow and BBB permeability experiments to permit the continuous withdrawal of arterial blood after isotope injection.

The procedures were timed so that all experiments were terminated by decapitation of the animal 3 hours after carotid ligation. The brain was quickly removed and a sample approximately 1 mm³ in size was taken bilaterally from the parietal cortex using a punch biopsy needle. These samples were placed in kerosene, and
the specific gravity was determined within 5 minutes using the bromobenzene–kerosene column technique of Nelson et al. The remaining brain was divided into the left and right cerebral hemispheres, the left and right diencephalon, the brainstem, and the cerebellum. The samples were quickly cleaned of external blood, the choroid plexus was discarded, and the brain tissue was placed into either preweighed crucibles for measurement of ion content or preweighed scintillation vials containing 1.5 ml of Protosol for determination of radiotracer content.

Specific gravity measurements on the samples of cortical gray matter were used to improve our selection of animals that had experienced significant ischemia. We excluded from the study any animal that had a specific gravity in the ischemic cortex within 2 SD of the mean specific gravity of the nonischemic hemispheres (1.0496 ± 0.010 SD). Use of this criterion lead to the exclusion of 2 animals that had been symptomatic 30 minutes after carotid ligation.

In some cases, experiments were conducted on gerbils subjected to a sham occlusion procedure. These animals were handled in exactly the same way except the carotid artery was not ligated or cauterized and there was no selection for neurologic symptoms.

Cerebral Blood Flow

The cerebral blood flow (CBF) was measured with [14C]butanol as described previously. The tracer was allowed to circulate for 15 seconds after i.v. injection before termination of the experiment by decapitation. An iterative technique was used to correct for the loss of tracer from brain tissue during the 15-second interval.

Water, Sodium, and Potassium Content

Brain samples were removed, placed in preweighed crucibles, and reweighed. The samples were then dried to constant weight in an oven at 100°C. The percent water content of the tissue was calculated by

\[
\text{water (％)} = \frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}} \times 100
\]

The dehydrated tissue samples were ashed in a muffle oven at 400°C for 16 hours. The residue was dissolved in 7 ml of 10% (v/v) nitric acid and diluted as necessary. The sodium and potassium concentration of each solution was then determined using flame photometry with lithium as the internal standard.

Blood and Plasma Volume of Brain

Regional brain plasma volume (PV) and red blood cell volume (RCV) were determined using a variation of the method described previously. Heparinized blood was collected by cardiac puncture of a donor gerbil, and the erythrocytes were separated and incubated for 30 minutes at 37°C with 300 μCi of 51Cr per 1.2 ml of packed cells. The labelled erythrocytes were washed 3 times with iced phosphate-buffered saline (PBS) and kept on ice. Just prior to use, an aliquot of cells was washed with PBS and suspended in PBS containing 1% bovine serum albumin (BSA) with 5 μCi of 123I-labelled BSA. A 0.05-ml bolus of the final suspension, having an hematocrit of 30–40%, was injected via the venous catheter. The isotopes were allowed to circulate for 2 minutes, then the animal was decapitated, and a terminal sample of blood was collected from the severed torso. Brain samples were dissolved in Protosol, and aliquots of whole blood and plasma from the final blood sample were dissolved in Protosol:ethanol (2:1 v/v). Radioactivity was determined in a two-channel liquid scintillation counter calibrated for simultaneous counting of the Auger and conversion electrons emitted by 31Cr and 125I.

PV, RCV, and blood volume (BV) were calculated as follows:

\[
PV (\text{ml/g}) = \frac{31\text{Cr}}{\text{g brain}} \times \frac{125\text{I}}{\text{ml blood}}
\]

\[
RCV (\text{ml/g}) = \frac{51\text{Cr}}{\text{g brain}} \times \frac{123\text{I}}{\text{ml blood}} \times \text{Hct} \times 0.976
\]

where Hct is the hematocrit of arterial blood and 0.976 was used to correct for the incomplete separation of plasma from red cells in the measurement of peripheral hematocrit.

\[
\text{BV (ml/g)} = PV + RCV
\]

\[
\text{tissue hematocrit (％)} = \frac{RCV}{BV} \times 100
\]

BBB Permeability to Sodium and Sucrose

The permeability of the BBB to 22Na and [3H]sucrose was determined by a modification of the technique of Ohno et al., which permits determination of the unidirectional rate of tracer uptake as the product of the tracer’s permeability (P) and the surface area (S) of the perfused capillary bed. The resulting value is known as the PS product. The principal modification in our procedure was the continuous withdrawal of arterial blood rather than intermittent sampling during the isotope circulation in order to obtain the integral of isotope concentration in the blood. This was accomplished with a peristaltic pump connected to PE-90 tubing glued to the PE-10 catheter in the left femoral artery. The PE-90 tubing contained a volume of heparinized saline that was approximately 50% greater than the amount of blood that would be withdrawn during the experiment.

A 0.05-ml solution of PBS containing 8 μCi of 22Na and 40 μCi of [3H]sucrose was injected as a bolus into the venous catheter. Coincident with the injection, the pump was activated to withdraw arterial blood at a rate of 0.010 ml/min, replacing the saline in the PE-90 catheter. After 20 minutes, the animal was decapitated and a blood sample was obtained from the severed torso for determination of the final concentrations of isotopes in the blood. The blood and remaining saline in the PE-90 catheter were expelled into a preweighed vial, the sample weight was determined, and an aliquot
was calculated using the total amount of isotope in the arterial blood sample (CJ, the withdrawal pump rate and C, is the amount of isotope in the arterial blood). The 3H and 22Na contents were determined using a two-channel liquid scintillation counter.

The PS product for each isotope was calculated as

\[
PS = \frac{C_{ev}}{\int C_{dt}}
\]

where \( C_{ev} \) is the amount of extravascular tracer in a tissue and \( C_{dt} \) is the amount of isotope in the arterial blood at time t. The integral of \( C_{dt} \) between the time of isotope injection and termination of the experiment was calculated using the total amount of isotope in the arterial blood sample (CJ), the withdrawal pump rate (FJ), and the arterial hematocrit (Hct):

\[
\int C_{dt} = \frac{C_{ev} (1 - Hct)}{FJ}
\]

The resulting value is expressed in terms of the plasma concentration since neither sodium nor sucrose appreciably enter red blood cells.

To calculate the amount of extravascular tracer in the brain, \( C_{ev} \), it is necessary to correct for the amount of tracer that was intravascular. This was done using the previously determined regional BV and the ratio of tissue to peripheral hematocrits (R) to calculate a regional PV:

\[
PV_{ac} = BV(1 - Hct \times R)
\]

Calculation of PV in this manner takes into account variability in the peripheral hematocrit between animals. Finally, \( C_{ev} \) was calculated from the total amount of isotope per gram of brain (\( C_{ev} \)) and the final concentration of isotope in the plasma (\( C_{p} \)).

\[
C_{ev} = C_{ev} - (C_{p} \times PV)
\]

Statistical Analysis
Results from sham-operated and experimental animals were compared using Student's t test for nonpaired data. Within a group of animals, results from the left and right sides were compared using Student's t test for paired data. Within a group of animals, results from the left and right sides were compared using Student's t test for paired data.

Radiopharmaceuticals
Fructose-1-3H]sucrose (10 Ci/mmol), n-[1-14C]butanol (1.0 mCi/mmol), 22Na, 51Cr (sodium chromate), and Protosol were purchased from DuPont-NEN (Boston, Mass.). [125I]albumin (bovine serum) (0.83 mCi/mg) was obtained from ICN Radiochemicals (Irvine, Calif.).

Results
Values for the physiological parameters obtained from sham-operated and experimental animals during the last half-hour of the experiment are shown in Table 1. There were no significant differences between the two groups.

Unilateral occlusion of the left common carotid artery caused a substantial reduction in CBF in the ipsilateral hemisphere compared with either the contralateral hemisphere or sham-operated animals (Table 2). The observed reduction in CBF is similar to that reported in other studies of unilateral occlusion in gerbils15 and is in the range that has been reported to cause significant brain edema.17 There was also a small but significant decrease in flow to the contralateral hemisphere compared with the sham-operated gerbils. Occlusion of the common carotid artery resulted in a significant reduction in CBF to the diencephalon; however, this decrease was not as great as that seen in the cerebral hemisphere. CBF in the contralateral diencephalon, the cerebellum, and the brainstem were unaffected by unilateral carotid occlusion.

As anticipated, unilateral carotid occlusion caused significant edema in the ipsilateral cerebral hemisphere with an increase in sodium and a decrease in potassium content of the tissue (Table 3). A similar change was observed in the ipsilateral diencephalon in spite of its greater residual flow compared to that in the cerebral hemisphere. This result suggests that unilateral carotid occlusion has a very heterogeneous effect on the diencephalon because one would not expect edema to develop if the entire tissue experienced a CBF of 42 ml/100 g/min. The sample we obtained probably contained brain tissue ranging from very ischemic to normal. It seems likely, therefore, that edema in the diencephalon sample was localized in only a portion of the sample. Nevertheless, the amount of water accumulated and the magnitudes of sodium gains and po-

### Table 1. Physiological Parameters

<table>
<thead>
<tr>
<th></th>
<th>Sham (n = 13)</th>
<th>Experimental (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MABP (mm Hg)</td>
<td>75 ± 7</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.33 ± 0.04</td>
<td>7.35 ± 0.05</td>
</tr>
<tr>
<td>PacO₂ (mm Hg)</td>
<td>42 ± 8</td>
<td>38 ± 6</td>
</tr>
<tr>
<td>PacO₂ (mm Hg)</td>
<td>71 ± 11</td>
<td>74 ± 19</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>34 ± 2</td>
<td>36 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SD.

### Table 2. Cerebral Blood Flow after 3 Hours of Unilateral Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemisphere</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>62.7 ± 8.6</td>
<td>49.9 ± 10.7</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>64.0 ± 8.1</td>
<td>13.5 ± 3.8†</td>
</tr>
<tr>
<td>Diencephalon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>106.1 ± 17.2</td>
<td>NS</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>99.1 ± 15.9</td>
<td>42.2 ± 12.7‡</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>96.3 ± 16.8</td>
<td>103.1 ± 26.8</td>
</tr>
<tr>
<td>Brainstem</td>
<td>116.4 ± 28.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SD for 6 determinations.

*Level of significance between groups using 2-tailed Student's t test for nonpaired samples. NS = no significant difference.

†p < 0.0001, ‡p < 0.001 compared with contralateral sample using 2-tailed Student's t test for paired samples.
tassium losses were similar in cerebral cortex and diencephalon (Table 4). Thus, we believe that, within the affected portion of the diencephalon, the development of brain edema was more severe than in the cerebral hemispheres.

The data shown in Table 3 indicate that the contralateral hemisphere and diencephalon of gerbils with unilateral carotid occlusion were identical to those of sham-operated animals with respect to water, sodium, and potassium contents. Therefore, the remaining experiments compared ipsilateral and contralateral structures of experimental animals rather than comparing experimental with sham-operated animals. The results shown in Table 5 indicate that RCV, PV, and consequently, BV of the ischemic cerebral hemisphere were reduced compared with the contralateral side. This decrease in BV was not observed in the diencephalon; however, there was a significant change in the tissue hematocrit in this region. In all samples, the tissue hematocrit was lower than the peripheral hematocrit, as reported previously.11,13

Although ischemia caused a reciprocal change in the amount of sodium and potassium in brain tissue, the increase in sodium was greater than the decrease in potassium (Table 4). This indicates a net influx of cations from blood to brain. To determine whether this increase in tissue sodium was the result of an increase in its rate of flux from blood to brain, we measured the PS products for sodium and sucrose. The latter was used to determine whether 3 hours of unilateral ischemia caused any generalized breakdown in the BBB to passage of small molecules since sucrose exposure to the brain by simple diffusion.18 As shown in Table 6, the PS product for sucrose was not affected by 3 hours of ischemia. In contrast, the PS product for sodium was reduced in the ipsilateral compared with the contralateral cerebral hemisphere. Since it is likely that both sodium and sucrose are exposed to the same brain capillary surface area (S), the ratio of their PS products is equivalent to the ratio of their permeabilities (P).

Our results indicate that, during ischemia, the P of the BBB to sodium was selectively reduced through a mechanism that did not affect sucrose P (Figure 1). This reduction in sodium P was seen in the cerebral hemisphere where ischemia was moderately severe, but not in the diencephalon where, on the average, ischemia was less severe.

The data in Table 6 and Figure 1 also indicate that the PS products for sodium and sucrose vary independently from region to region. Thus, the PS product for sodium is lowest and for sucrose is highest in the diencephalon of all nonischemic brain regions. This observation suggests that the BBB permeabilities of these two solutes are influenced by different factors, as would be expected if sodium but not sucrose moves across the brain capillaries by a carrier-mediated process.19 In this situation, one would expect that region-to-region variation in the PS product for sucrose would be influenced largely by differences in capillary surface area while the PS product for sodium would be influenced by the density of transporters as well as by capillary surface area.

### Discussion

Brain edema, defined as an increase in brain water content leading to an increase in brain volume, develops in a variety of pathological conditions. Klatzo20 classified brain edema into two major categories: vasogenic and cytotoxic. To these, Fishman21 added interstitial brain edema as a distinct entity. This widely accepted classification system is based on the mechanisms by which brain edema is believed to form. Thus, vasogenic edema develops when the permeability of the BBB is increased and fluid accumulates in the interstitial space. This term is most often used when

### Table 3. Water, Sodium, and Potassium Content of Brain After 3 Hours of Unilateral Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Cerebral hemisphere</th>
<th>Diencephalon</th>
<th>Brainstem</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham</td>
<td>Experimental</td>
<td>Sham</td>
<td>Experimental</td>
</tr>
<tr>
<td>Water (% wet wt)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>79.2 ± 0.6</td>
<td>NS</td>
<td>76.1 ± 0.7</td>
<td>72.9 ± 1.9</td>
</tr>
<tr>
<td>Contralateral</td>
<td>79.0 ± 0.6</td>
<td>0.001</td>
<td>76.8 ± 0.7</td>
<td>72.9 ± 1.9</td>
</tr>
<tr>
<td>Sodium (mEq/kg dry wt)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>234 ± 16</td>
<td>NS</td>
<td>218 ± 14</td>
<td>193 ± 23</td>
</tr>
<tr>
<td>Contralateral</td>
<td>231 ± 17</td>
<td>0.0001</td>
<td>208 ± 14</td>
<td>213 ± 17</td>
</tr>
<tr>
<td>Potassium (mEq/kg dry wt)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>441 ± 15</td>
<td>NS</td>
<td>374 ± 20</td>
<td>381 ± 25</td>
</tr>
<tr>
<td>Contralateral</td>
<td>438 ± 17</td>
<td>0.0001</td>
<td>354 ± 56</td>
<td>381 ± 25</td>
</tr>
</tbody>
</table>

Values are means ± SD derived from data in Table 3. *Level of significance between groups using 2-tailed Student's t test for nonpaired samples. NS = no significant difference. **t < 0.0001, †p < 0.0001, ‡p < 0.01 compared to contralateral sample using 2-tailed Student's t test for paired samples.

### Table 4. Changes in Water and Ion Content of the Brain After 3 Hours of Unilateral Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Cerebral hemisphere</th>
<th>Diencephalon</th>
<th>Brainstem</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham</td>
<td>Experimental</td>
<td>Sham</td>
<td>Experimental</td>
</tr>
<tr>
<td>ΔWater (I/kg)</td>
<td>0.46 ± 0.10</td>
<td>165 ± 60</td>
<td>146 ± 18</td>
<td>165 ± 60</td>
</tr>
<tr>
<td>ΔNa (mEq/kg)</td>
<td>146 ± 18</td>
<td>-107 ± 17</td>
<td>165 ± 60</td>
<td>-107 ± 17</td>
</tr>
<tr>
<td>ΔK (mEq/kg)</td>
<td>-107 ± 17</td>
<td>38 ± 13</td>
<td>-114 ± 47</td>
<td>38 ± 13</td>
</tr>
<tr>
<td>ΔNa + ΔK (mEq/kg)</td>
<td>146 ± 18</td>
<td>-107 ± 17</td>
<td>165 ± 60</td>
<td>-114 ± 47</td>
</tr>
</tbody>
</table>

Values are means ± SD derived from data in Table 3.
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...the BBB becomes leaky to plasma proteins. In cytotoxic edema, BBB permeability is grossly normal, but the cellular elements of the brain become swollen. This is believed to result from an interference with the active pumping of ions across cell membranes and a subsequent uptake of sodium and loss of potassium by the cells. Initially, the cells swell at the expense of the fluid spaces within the brain but no net increase in water content. Ultimately, there must be additional exchanges of salt and water between the brain and blood to account for edema formation. The third type of brain edema, interstitial edema, occurs when the normal outflow of cerebrospinal fluid (CSF) is obstructed and fluid is forced into the periventricular brain tissue.

In actual pathologic conditions, these various types of brain edema may occur together. This is especially true in ischemia, and it has been proposed that ischemic brain edema warrants separate classification. Ischemic brain edema is believed to be cytotoxic initially because the BBB permeability is grossly intact. Later, the barrier to plasma proteins breaks down, and a vasogenic phase of edema is recognized. Our investigation was directed toward a better understanding of the processes involved in the early phase of ischemic brain edema. We were particularly interested in the edema that develops during partial ischemia rather than during complete ischemia followed by reperfusion.

Previous studies show a good correlation between increases in brain sodium and water during partial ischemia. A decrease in brain potassium is also frequently observed. When ischemia lasts more than 1 hour, the increase in brain sodium exceeds the decrease in brain potassium and, thus, there is a net increase in the principal brain cations. Since permeability of the BBB to sodium is normally quite low, the mechanism for a marked increase in tissue sodium when the BBB is thought to be intact is not clear. Some investigators have postulated that, as the cellular sodium pump fails, sodium moves from the brain interstitial fluid into the brain cells, which creates a gradient for the diffusion of sodium from blood to brain. Other investigators speculate that the active transport of sodium from blood to brain across the brain capillaries is specifically stimulated during the early phase of ischemia.

Our studies are the first to test these hypotheses directly. In agreement with other studies, we found a marked increase in brain water and sodium and a net increase in brain cations 3 hours after unilateral cerebral ischemia in gerbils. In spite of the large increase in tissue sodium, there was no increase in the permeability of the BBB to sodium at the end of the 3-hour ischemic period. In fact, we observed a significant decrease in sodium permeability when the general permeability of the BBB to small molecules was unchanged. Thus, the increase in brain sodium content is not due to an increase in sodium uptake. We conclude that sodium accumulates in brain tissue because of reduced clearance of the sodium that normally moves from blood to brain.

The schematic diagram shown in Figure 2 presents a model for the development of ischemic brain edema which takes our findings into account. Normally, there is a continuous flow of salt and water from blood to brain. Recent studies indicate that the influx of sodium into the brain is mediated by distinct transport systems that first allow sodium to cross the luminal membranes of brain capillary endothelial cells and then actively pump it out of the endothelial cells into the brain. The latter step is mediated by Na, K-ATPase, which in...
potassium ions for a net cation movement out of the
cells. The potassium that enters the endothelial cells
could then exit down a concentration gradient either
into the blood or the brain; however, the nature of this
process has not been determined. The net effect of
these coupled sodium transport systems is to move
cations from blood to brain. Chloride will follow to
maintain electroneutrality and water, to maintain
isosmolality.

In spite of a continuous influx of water, brain vol-
ume normally remains constant. This indicates the ex-
istence of mechanisms for the clearance of the fluid.
One likely clearance pathway is bulk flow of fluid
through the brain’s interstitial space into the CSF (Fig-
ure 2). Cserr and coworkers24,25 have estimated the rate
of flow of interstitial fluid out of the brain to be be-
tween 0.11 and 0.29 μl/g/min in the caudate nucleus,
midbrain, and brainstem. Alternatively, a portion of
the sodium and water that enters the brain may return
across the capillaries into the blood. Although the exis-
tence of such a pathway has not been studied, the
presence of transport systems that could allow sodium
to enter the endothelial cells from the interstitial fluid
have been described.26,27

During ischemia, there is an early reciprocal shift of
sodium and potassium between the brain cells and the
interstitial fluid, resulting in a reduction in the volume
of and an increase in the resistance to flow through the
interstitial space. This in turn should impede the nor-
mal bulk flow of fluid through these spaces and, if
fluid production by the capillaries remains normal,
edema will develop. Thus, a decrease in the clearance
rate of isotonic fluid secreted by the brain capillaries
would lead to brain edema. The second possible pathway for sodium
clearance, return to the blood, could also be blocked
and cause brain edema. At present we do not know
which clearance pathway is reduced in ischemia; how-
ever, we believe that blockage of bulk flow is more
likely.

Several of our findings provide additional support
for this hypothesis. The reduction in sodium uptake
with no change in sucrose uptake can only be ex-
plained if sodium enters the brain by specific transport
pathways. Since active transport is an important part of
transcapillary sodium flux, it is not surprising to see a
reduction in this energy-requiring step during ischemia
(discussed below). In addition, the changes in brain
water, sodium, and potassium contents (Table 3) pro-
vide information on the rate of formation and the com-
position of the edema fluid that is produced (Table 7).

The ratio of sodium gained to potassium lost in the
cortex is 1.37, very similar to the theoretical value of
1.5 if 3 sodium molecules enter while 2 potassium
molecules leave via Na, K-ATPase. The difference
could be explained by either loss of some potassium to
CSF or return of sodium to the blood from the brain
(Figure 2). The apparent sodium content of edema
fluid is 0.5—0.6 times that of plasma. Since the fluid
secreted from the blood to the brain is likely to be
isotonic, this result suggests that, in partial ischemia,
approximately half of the water enters the brain in
response to an increase in osmoles other than sodium,
and the other half enters the brain as isotonic fluid. The
apparent rate of accumulation of this isotonic fluid
over the 3-hour period is 0.26 μl/g/min, very similar to
the normal rate of bulk flow of interstitial fluid.24,25

Finally, assuming that sodium accumulation occurs at
a constant rate throughout the 3 hours of ischemia,22
the rate of increase in sodium content of the ischemic
compared with the nonischemic hemisphere can be
used to calculate a PS product for the net accumulation
of sodium in the brain. The calculated value of
0.97 ± 0.11 μl/g/min is 59% of the observed PS prod-
uct for unidirectional sodium uptake. Thus, some of
the sodium that entered the brain during ischemia must
have been cleared, either directly to the blood or to
CSF.

| Table 7. Derived Values for Edema Formed During 3 Hours of Unilateral Ischemia |
|---------------------------------|------------------|------------------|------------------|------------------|
|                                | Apparent         | Rate of          | Apparent         | Net PS           |
|                                | sodium conc.     | edema fluid      | sodium fluid     | for sodium       |
|                                | of edema fluid   | accumulation     | secretion        | (μl/g/min)       |
|                                | (mEq/l)          | (μl/g/min)       | (μl/g/min)       | (μl/g/min)       |
| Cerebral hemisphere            | 1.37 ± 0.15      | 85 ± 27          | 0.49 ± 0.11      | 0.26 ± 0.08      | 0.97 ± 0.11 |
| Diencephalon                   | 1.54 ± 0.38      | 99 ± 42          | 0.58 ± 0.25      | 0.38 ± 0.27      | 1.22 ± 0.43 |

Values are means ± SD derived from data of Tables 3 and 4.
Two possible sources of error in our measurements warrant further consideration. Uptake of isotopes was measured over 20 minutes, and it is possible that some of the isotope that entered the brain was lost to the blood during this interval. However, this cannot explain the reduction in sodium permeability in the ischemic hemisphere since the sodium distribution space is greater in that region than in the control hemisphere, and, therefore, backflux should be delayed. An additional source of error is the exchange of ions and isotopes between brain and CSF. To some extent, the CSF could provide a source of sodium and a sink for potassium, and the changes in tissue ion content would not totally represent exchange across the BBB. Radioactive sodium might also enter the brain from the CSF after being pumped across the choroid plexus. Without measurement of CSF ion and radioisotope content, it is not possible to determine the magnitude of these errors.

The PS product for sodium was significantly reduced in the cerebral hemisphere but not the diencephalon (Table 6). Nevertheless, similar degrees of edema developed in the two structures (Table 3). For reasons discussed earlier, we believe that only part of the diencephalon was ischemic but that edema was worse in the ischemic portion of the diencephalon than it was in the cortex. It is, therefore, possible that the reduced sodium permeability in the cortex helped to limit the extent of brain edema formation. In addition, a reduction in BBB sodium transport at very low flows could explain the results of Crockard et al, where edema became more severe as flow decreased from 0.2 to 0.07 ml/min but then became less severe at lower flows.

We can only speculate on the mechanism for the decrease in BBB sodium transport during severe ischemia. A reduction in capillary Na, K-ATPase activity is a likely possibility. This could occur as a result of either a failure in capillary energy metabolism or possible damage to the transporter itself. In this regard, we have recently observed a specific decrease in brain capillary Na, K-ATPase activity when brain capillaries are exposed to free radicals. An alternative mechanism for the reduction in the sodium PS product is

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**Figure 2.** Proposed flow of water and sodium from blood to brain to CSF. In the normal brain, sodium from plasma crosses the endothelial cells by sequential transport across the luminal and antiluminal membranes. This process occurs in exchange for potassium in the interstitial fluid, which may then either enter the blood or be recycled back to the brain (- - - -). Water follows to maintain osmotic equilibrium. Once sodium reaches the brain's interstitial space, it is cleared by bulk flow with water through the interstitial space, or it may possibly return to the blood if appropriate transport systems are present in the endothelial cells ( - - - - -). In ischemia, the brain cells swell and reduce the size of the interstitial spaces. Consequently, the bulk flow of sodium and water into the CSF is impeded and edema develops. Alternatively, sodium may accumulate in the brain if its return to the blood is blocked. In either case, ischemic brain edema would result from reduced clearance of salt and water secreted by the brain capillaries.
inhibition of the transport systems that allow sodium to cross the luminal membranes of the endothelial cells.

In conclusion: Our results indicate that the permeability of the BBB to sodium is not increased after 3 hours of cerebral ischemia. The increase in brain sodium and water seen during ischemia must, therefore, result from a reduced clearance of sodium from the brain, possibly by obstruction of bulk flow of interstitial fluid. While we did not directly measure the clearance of sodium from ischemic brain tissue, our results suggest that such studies are warranted. In addition, we speculate that, in severe ischemia, the rate of formation of brain edema is reduced because active transport of sodium from the blood to the brain is reduced. Since specific agents that block the transport of sodium across the luminal membranes of capillaries are available, it may be possible to control the edema seen in early ischemia with pharmacologic agents.

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References


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