Ischemic Brain Edema Following Occlusion of the Middle Cerebral Artery in the Rat. I: The Time Courses of the Brain Water, Sodium and Potassium Contents and Blood-Brain Barrier Permeability to 125I-Albumin


SUMMARY The present study was undertaken to analyze the roles of brain cations and of the blood-brain barrier (BBB) to albumin in the development of ischemic brain edema. Using the rat middle cerebral artery (MCA) occlusion model, changes in the brain water, sodium, and potassium contents were followed for a period of seven days. The permeability of the BBB to proteins was also followed by 125I-albumin transfer from the blood into the brain. A significant edema developed as early as three hours after MCA occlusion. This progressed rapidly to reach a maximum on the third day, gradually regressing thereafter. The increase in the brain water contents showed a parallel time course to the increase in the sodium and decrease in the potassium contents. A significant increase in the BBB permeability to albumin occurred 72 hours after MCA occlusion. However, there was no correlation between the brain water content and BBB permeability to albumin in the hemispheres studied 72 hours after MCA occlusion. The correlation between the brain water and sodium contents was not clear during the first six hours, but became highly significant thereafter. The data suggest that an increase in the BBB permeability to sodium occurred 12-48 hours after MCA occlusion, which, together with an antecedent intracellular shift of sodium, resulted in a massive influx of water and sodium into the brain. The BBB permeability change to sodium, not to proteins, seems to play a predominant role in the pathogenesis underlying ischemic brain edema.

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CLINICAL AND EXPERIMENTAL STUDIES have indicated that cerebral edema, defined as an increase in brain tissue volume resulting from an increase in its fluid contents, develops following acute regional cerebral ischemia and can cause mass effect and herniation, which in turn aggravate the primary ischemic injury to the brain. The edema that is observed in the ischemic brain has a characteristic time course, and this justifies a separate pathological entity as ischemic cerebral edema. It begins with a cytotoxic phase in which, due to energy failure after cessation of the cerebral circulation, intracellular fluid accumulation occurs in association with the shifts of sodium and potassium between intra- and extracellular compartments in the brain. At this stage, the permeability of the blood-brain barrier (BBB) to serum proteins is not changed. When this happens, it heralds the phase of vasogenic edema. However, the role of the BBB breakdown to proteins in relation to accumulation of fluid has not been established. In view of the complicated pathological process involved, elucidation of the mechanisms of ischemic edema requires an analysis of pathogenic factors, both in the acute and in the chronic phases of ischemia. Most experimental studies, however, have dealt only
with the relatively early stages of ischemia, partly because there are difficulties in maintaining survival of animals after some ischemic insults. We have therefore used the occlusion of the middle cerebral artery (MCA) in rats as an animal model to investigate ischemic edema. The unilateral, permanent occlusion of the MCA in rats produces a consistent focal ischemic lesion. In addition, the relative ease of operative technique and of obtaining post-operative chronic survival makes it possible to perform a study with a large number of animals.

We have used this animal model to measure brain water, sodium, and potassium contents in the chronic as well as in the acute phases of ischemia. Several reports implicate the role of the movement of electrolytes in the development of ischemic edema but the precise nature of their involvement in the process of edema progression and resolution remains to be clarified. The BBB permeability to albumin was also evaluated quantitatively. The role of these factors in the pathogenesis of ischemic edema was discussed.

Materials and Methods

Surgical Preparation
Male Sprague-Dawley rats, weighing 250-350 grams, were anesthetized by inhalation of 2% halothane. The proximal portion of the left MCA was permanently occluded by a microsurgical technique. The animals underwent a left subtemporal craniectomy after partial removal of the temporalis muscle. Using a microbipolar unit (Mizuho-Ika, Tokyo), the exposed MCA was electrocauterized just medial to the olfactory tract and was severed to assure the completeness of the vascular occlusion. In sham-operated animals, the surgical procedure was carried out in a similar manner, except for the electrocauterization and severance of the exposed MCA. After closure of the surgical wound, the animals were returned to their cages and permitted free access to food and water. The systemic arterial blood pressure (SABP), rectal temperature, and body weight were measured daily until sacrifice. The SABP was measured by the non-invasive plethysmographic tail-cuff method. Each animal was sacrificed according to the schedule described below.

Measurements of the Brain Water, Sodium and Potassium Contents

Brain edema was determined by comparison of wet and dry weight. Rats were sacrificed at three, six, 12, 24, 48, 72, 96 and 168 hours after MCA occlusion at the rate of seven to 14 animals at each time point. Sham-operated rats were sacrificed at 24, 48, 72, 96 and 168 hours after the surgery, five to seven animals at each time point. At the time of sacrifice, normal, non-operated rats (N = 5-7) were always included in order to assess the stability of the wet and dry methods as well as the electrolyte measurements. Therefore, the number of normal control animals became relatively large.

The rats were decapitated, and the brains were quickly removed. The wet weight of each hemisphere was measured on a chemical balance (Mettler HSL2) within 90 seconds after decapitation. After drying the brain in an oven at 105°C for five days, the dry weight was obtained. Separate studies indicated that the dry weight of the hemisphere decreased gradually until five days after desiccation under these conditions and was stable thereafter. The water contents of each hemisphere were calculated as follows:

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

After homogenizing the dried brain, sodium and potassium ions were extracted with 0.75 N HNO₃. The cation contents of each hemisphere were measured by flame photometry and expressed as Meq/kg, dry weight.

Transfer of ¹²⁵I-albumin from the Blood into the Brain

The BBB permeability was quantitatively evaluated by the transfer of ¹²⁵I-bovine serum albumin (¹²⁵I-BSA, New England Nuclear Corp., Massachusetts) from the blood into the brain. Seven MCA-occluded and five sham-operated rats each were sacrificed at 24, 48, 72, 96 and 168 hours postoperatively. Six normal rats were also sacrificed.

Two hours before sacrifice, the animals received 10 µCi of ¹²⁵I-BSA via the tail vein. Immediately before sacrifice, blood samples were collected and then the cerebral vasculature was flushed with 0.9% saline introduced from the asending aorta to the right atrium at 120 cm H₂O pressure. The ¹²⁵I radioactivities of plasma and of each cerebral hemisphere were measured with a scintillation counter. Transfer of ¹²⁵I-BSA from the blood into the brain was expressed as follows:

\[
\text{¹²⁵I-BSA transfer} = \frac{125^I \text{ cpm} / \text{g brain}}{125^I \text{ cpm} / \text{g plasma}} \times 10^3
\]

Simultaneous Measurements of Edema and BBB Permeability to Albumin

The brain water contents and ¹²⁵I-BSA transfer from the blood into the brain were measured simultaneously in 13 rats after 72 hours of MCA occlusion. Two hours before sacrifice, the animals received 10 µCi of ¹²⁵I-BSA via the tail vein. Blood samples were taken immediately before sacrifice. Without saline perfusion of the cerebral vascular system, the animals were decapitated and the brains were removed. Both the brain water contents and ¹²⁵I-BSA passage from the blood into the brain were determined in an individual sample in the same way as already described. The correlation between edema and BBB permeability to albumin was studied by regression analysis.

Statistical Evaluation

Values are expressed as means ± SEM. The statistical significance of differences between group means
was evaluated by Student’s unpaired two-tail t-test. A p value of less than 0.05 was considered significant.

### Results

**General Preparation**

Following MCA occlusion, definite neurological deficits, such as disturbed consciousness or hemiparesis, were not recognized. The only change was that spontaneous movement of the animals seemed depressed. The behavior of the sham-operated animals appeared quite normal. Out of 112 animals with MCA occlusion, one died three days after surgery and was excluded from the results. The cause of the death was confirmed. No death occurred in the sham-operated group.

The post-operative systemic conditions are shown in table 1. A moderate reduction of the SABP was observed one hour after the operation, and this condition persisted until sacrifice. The rectal temperature showed a course similar to the SABP. There was a significant and progressive reduction of body weight after MCA occlusion. In the sham-operated group, the reduction of body weight was also observed, but to a lesser degree than in the MCA-occluded group. It was suggested that the body weight loss observed after MCA occlusion was caused by some neurological events as well as mechanical impairment of mastication related to the surgical damage to the temporalis muscle.

**The Brain Water, Sodium and Potassium Contents**

In the normal, non-operated animals, the hemispheric water, sodium and potassium contents were 79.62 ± 0.03 (%), 334 ± 7 (mEq/kg, d.w.), and 517 ± 6 (mEq/kg, d.w.), respectively.

The values of the brain water, sodium, and potassium contents in the left and right hemispheres of the normal, sham-operated, and MCA-occluded groups at each period are shown in table 2.

The time course of the brain water contents after MCA occlusion is illustrated in figure 1A. The brain water contents were observed to increase as early as

### Table 1 Post-operative Changes in Systemic Conditions

(A) Systemic arterial blood pressure (SABP) and rectal temperature in the MCA-occluded animals.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>0 hr</th>
<th>1 hr</th>
<th>1 day</th>
<th>2 day</th>
<th>3 day</th>
<th>4 day</th>
<th>7 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABP (mm Hg)</td>
<td>119 ± 4</td>
<td>104 ± 4</td>
<td>105 ± 2</td>
<td>105 ± 3</td>
<td>109 ± 3</td>
<td>108 ± 3</td>
<td>114 ± 4</td>
</tr>
<tr>
<td>Temp. (°C)</td>
<td>38.2 ± 0.2</td>
<td>36.7 ± 0.3</td>
<td>37.4 ± 0.2</td>
<td>37.9 ± 0.3</td>
<td>37.1 ± 0.2</td>
<td>36.8 ± 0.2</td>
<td>37.8 ± 0.3</td>
</tr>
</tbody>
</table>

(B) Body weight (gram) in the MCA-occluded and sham-operated animals.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>0 day</th>
<th>1 day</th>
<th>2 day</th>
<th>3 day</th>
<th>4 day</th>
<th>5 day</th>
<th>6 day</th>
<th>7 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA-occlusion</td>
<td>294 ± 3</td>
<td>270 ± 3</td>
<td>260 ± 4</td>
<td>260 ± 7</td>
<td>256 ± 9</td>
<td>252 ± 12</td>
<td>249 ± 14</td>
<td>244 ± 17</td>
</tr>
<tr>
<td>(% Decrease)</td>
<td>(8.0 ± 0.6)</td>
<td>(11.4 ± 1.1)</td>
<td>(11.6 ± 1.9)</td>
<td>(12.8 ± 2.6)</td>
<td>(14.2 ± 3.6)</td>
<td>(15.2 ± 4.2)</td>
<td>(17.1 ± 5.5)</td>
<td></td>
</tr>
<tr>
<td>Sham-operation</td>
<td>273 ± 3</td>
<td>262 ± 3</td>
<td>253 ± 4</td>
<td>249 ± 5</td>
<td>249 ± 5</td>
<td>256 ± 5</td>
<td>258 ± 5</td>
<td>258 ± 5</td>
</tr>
<tr>
<td>(% Decrease)</td>
<td>(4.1 ± 0.7)</td>
<td>(7.3 ± 1.0)</td>
<td>(8.7 ± 1.3)</td>
<td>(8.7 ± 1.4)</td>
<td>(8.7 ± 1.5)</td>
<td>(6.3 ± 1.7)</td>
<td>(5.4 ± 1.6)</td>
<td></td>
</tr>
</tbody>
</table>

Values are the mean ± SEM of seven animals.

### Table 2 The Brain Water, Sodium and Potassium Contents in the Left and Right Hemispheres

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Left hemispheres</th>
<th>Right hemispheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>H2O (%)</td>
<td>Na (mEq/kg)</td>
</tr>
<tr>
<td>Sham</td>
<td>79.62 ± 0.03(47)</td>
<td>334 ± 7(42)</td>
</tr>
<tr>
<td>24 hr.</td>
<td>79.56 ± 0.10(7)</td>
<td>323 ± 10(7)</td>
</tr>
<tr>
<td>48 hr.</td>
<td>79.53 ± 0.07(7)</td>
<td>297 ± 8(7)</td>
</tr>
<tr>
<td>72 hr.</td>
<td>79.67 ± 0.06(7)</td>
<td>315 ± 8(7)</td>
</tr>
<tr>
<td>96 hr.</td>
<td>79.74 ± 0.10(5)</td>
<td>304 ± 12(7)</td>
</tr>
<tr>
<td>7 days</td>
<td>79.55 ± 0.08(7)</td>
<td>308 ± 9(7)</td>
</tr>
<tr>
<td>MCA</td>
<td>80.41 ± 0.11(7)†‡</td>
<td>346 ± 13(7)</td>
</tr>
<tr>
<td>6 hr.</td>
<td>80.25 ± 0.08(7)†‡</td>
<td>355 ± 19(7)</td>
</tr>
<tr>
<td>12 hr.</td>
<td>80.78 ± 0.23(7)†‡</td>
<td>403 ± 23(7)†‡</td>
</tr>
<tr>
<td>24 hr.</td>
<td>82.10 ± 0.19(7)†‡</td>
<td>542 ± 25(7)†‡</td>
</tr>
<tr>
<td>48 hr.</td>
<td>83.27 ± 0.23(14)‡</td>
<td>608 ± 38(14)‡</td>
</tr>
<tr>
<td>72 hr.</td>
<td>83.88 ± 0.76(7)‡</td>
<td>713 ± 54(7)‡</td>
</tr>
<tr>
<td>96 hr.</td>
<td>82.76 ± 0.29(7)‡</td>
<td>509 ± 32(7)‡</td>
</tr>
<tr>
<td>7 days</td>
<td>81.87 ± 0.31(7)‡</td>
<td>508 ± 23(7)‡</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01, ‡p < 0.001 (Student’s t-test).
three hours after MCA occlusion (80.41 ± 0.11, N = 7, p < 0.001). It showed a further progressive increase thereafter, reaching a maximum on the second (83.27 ± 0.23, N = 14, p < 0.001) and the third (83.88 ± 0.76, N = 7, p < 0.001) days. It then started to decrease after the fourth day (82.76 ± 0.29, N = 7, p < 0.001), although the water contents on the seventh day (81.87 ± 0.31, N = 7) was still significantly higher than the preoperative value, p < 0.001. In the contralateral hemisphere, there was no significant increase in the water contents, except on the seventh day (79.83 ± 0.07, N = 7), when it was significantly higher than the normal control (p < 0.05).

The time course of the brain sodium contents after MCA occlusion proved to parallel that of water (fig. 1B). On the other hand, a reversed relationship was observed between the potassium contents and the water and sodium contents (fig. 1C). The electrolyte contents showed no significant changes in the contralateral hemisphere, except that the potassium contents after 24 hours of ischemia (570 ± 15, N = 7) was significantly higher than normal control (p < 0.01).

To seek a possible relationship between the water and sodium contents, each value in an individual specimen was plotted at each period after MCA occlusion. A significant correlation between the two parameters was not evident within six hours, but was observed at 12, 48, 96, and 168 hours after MCA occlusion (fig. 2). When all data were plotted together, a significant linear correlation between the water and sodium contents was demonstrated (r = 0.8773, p < 0.005, fig. 3). Although there was rather wide scattering of data, there was also a significant correlation between the water contents and the decrement of the potassium contents (r = 0.6843, p < 0.005, fig. 4). The decrement of potassium was calculated as the difference between its actual value and the mean value of the normal control.

Transfer of 125I-albumin from the Blood into the Brain

The time course of the BBB permeability to albumin is shown in figure 1D. At each period after the sham operation, a small but significant increase in 125I-albumin transfer was observed, reflecting cortical damage related to craniectomy. This increase was almost constant throughout the observation period. Increased 125I-albumin transfer was shown after 24 and 48 hours of MCA occlusion, but the values did not differ significantly from those in the sham-operated group. Therefore, this increase in 125I-albumin transfer was considered to be due to cortical damage during craniectomy, not to the MCA occlusion itself. On the other hand, a marked increase in 125I-albumin transfer was demonstrated after three days of ischemia, when it was sig-
increased BBB permeability to albumin due to MCA occlusion per se was not evident until three days after ischemia.

Simultaneous measurements of the brain water contents and BBB permeability to albumin in 13 rats three days after MCA occlusion did not show a significant correlation between these two parameters (r = 0.006, fig. 5).

The Net Gain or Loss of Water and Electrolytes

The net gain or loss of water and electrolytes in the ischemic hemisphere (ΔH₂O, ΔNa, and ΔK) can be calculated as differences from the normal values. Their values calculated from mean values at each period (table 2) are shown in table 3. The ratios of ΔNa/ΔH₂O, (ΔNa-ΔK)/ΔH₂O, and ΔNa/ΔK are also shown in table 3.

Discussion

Experimental Model

Ischemic cerebral edema is one of the major factors complicating the primary ischemic insult, and is of great clinical importance in the management of stroke. Because of this, its mechanisms and treatments have

![Figure 2. The correlation between the brain water and sodium contents at each time after MCA occlusion.](image-url)

![Figure 3. The correlation between the brain water and sodium contents throughout the experimental period.](image-url)
been investigated using various animal models of cerebral ischemia. Those models involve different animal species and operative procedures to induce ischemia, in which there are both advantages and disadvantages.

The present model of focal cerebral ischemia produced by MCA occlusion in rats provides a reproducible, consistent lesion assessed by changes in histopathology and cerebral blood flow. The operative procedure is relatively simple, although some skill in microsurgery is needed. Post-operative mortality is almost negligible, and survival for a few weeks is easily achieved. Therefore, a sufficient number of animals to warrant statistical analysis can be used for the investigation of its consequences.

The time courses of the brain water, sodium and potassium contents, as well as of the BBB permeability to albumin during seven days following MCA occlusion were delineated in the present study (fig. 1). The temporal profile of ischemic brain edema thus shown is in accord with the results reported in experimental animals and in human strokes. In the sham-operated animals, on the other hand, changes in the brain water, sodium, and potassium contents were not evident, whereas some increase in the BBB permeability to albumin was observed due to cortical damage at the site of surgery. The increase in the BBB permeability to albumin after sham operation was almost constant throughout the experimental period, so that the increased BBB permeability due to the MCA occlusion could be estimated by subtracting the values in the sham-operated group from those in the MCA-occluded group. Thus, the present model of MCA occlusion in rats is considered to be suitable for the study of cerebral edema due to regional ischemia.

Time Courses of Brain Edema and BBB Permeability to Albumin

Brain edema, assessed by an increase in the brain water contents, began to develop as early as three hours after MCA occlusion (table 2). The increase progressed rapidly to a maximum on the second and third days. Subsequently, the edema started to regress gradually. In the contralateral hemisphere, significant edema was observed only on the seventh day.
The changes in the BBB permeability to albumin, quantified by $^{125}$I-albumin transfer from the blood into the brain, showed a different pattern from that of edema. Increased BBB permeability to albumin was not evident until the third day after the operation, when the edema progression had already become maximal. A separate experiment measuring the brain water contents and the BBB permeability to albumin in the same sample revealed no correlation between these parameters three days after MCA occlusion (fig. 5). It is generally agreed that vasogenic edema is a relatively late event in the development of ischemic edema. The present results, showing a time course parallel to that of the water concentration in the serum (table 3), it may be argued that the movement of sodium and water across the BBB were closely related to each other throughout the development of ischemic brain edema (fig. 3). This finding is consistent with previous reports showing a similar correlation between the brain water and sodium contents at various periods following ischemia. Regarding the potassium contents, a correlation with the water contents was also revealed, though it was less marked than in the case of sodium. Since close correlations between the brain water and electrolyte contents were demonstrated, a more detailed analysis of the data was carried out to investigate the mechanism underlying ischemic brain edema.

In the early stage of ischemia, namely three to six hours after MCA occlusion, the changes in the brain sodium and potassium contents were small and not significantly different from the control values, whereas the increase in the brain water contents was already significant (table 2). On the assumption that $\Delta K$, namely the loss of intracellular potassium, is replaced by an equivalent amount of sodium, the ratio of $(\Delta Na - \Delta K)/\Delta H_2O$ represents the sodium concentration of the edema fluid. The values of $(\Delta Na - \Delta K)/\Delta H_2O$ were far below the serum concentration of sodium in this period (table 3). This indicates that the sodium influx occupies only a part of brain osmoles that caused the water influx. Previously suggested mechanisms, such as increased osmotic activity of sodium and the hydrostatic pressure gradients between the peripheral patent vascular lumen and the central ischemic zone, may well be responsible for the water influx at the beginning of ischemic brain edema. However, it may be pointed out that the changes in the brain water and electrolyte contents in this period were relatively small compared to those occurring in later periods.

At 12–48 hours, the increases in the brain water and sodium contents were pronounced, and their correlation became increasingly significant (fig. 2). Since the values of $(\Delta Na - \Delta K)/\Delta H_2O$ exceeded the sodium concentration in the serum (table 3), it may be argued that the edema fluid became hypertonic to serum in this period. If so, the sodium influx across the BBB must be explained by an active transport mechanism. However, such an argument seems of questionable value, because the values of $(\Delta Na - \Delta K)/\Delta H_2O$ do not necessarily represent the sodium concentration of actual edema fluid. Redistribution of water and electrolytes into various compartments of the brain must be taken into account before such a calculation is made. In this regard, Hossmann et al. reported that, following complete cerebral ischemia of one hour’s duration in cats, the intracellular uptake of sodium during ischemia amounted to 139 mEq/kg, d.w., whereas the intracellular release of potassium was only 64 mEq/kg, d.w. With this intracellular influx of sodium, the subarachnoid sodium activity dropped from the normal value of 133 mEq/L to 53 mEq/L, in spite of a net increase in the brain sodium contents. Although the pathophysiology of regional ischemia differs from that of complete ischemia, a similar intracellular influx of sodium was shown to occur following MCA occlusion in cats. In

**TABLE 3** The Net Changes in Hemispheric Contents of Water, Sodium, and Potassium

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>$\Delta H_2O$ (L/kg, d.w.)</th>
<th>$\Delta Na$ (mEq/kg, d.w.)</th>
<th>$\Delta K$ (mEq/kg, d.w.)</th>
<th>$\Delta Na/\Delta H_2O$</th>
<th>$(\Delta Na - \Delta K)/\Delta H_2O$</th>
<th>$\Delta Na/\Delta K$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 hrs</td>
<td>0.205</td>
<td>12</td>
<td>6</td>
<td>59</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>6</td>
<td>0.163</td>
<td>21</td>
<td>8</td>
<td>129</td>
<td>80</td>
<td>2.6</td>
</tr>
<tr>
<td>12</td>
<td>0.303</td>
<td>69</td>
<td>53</td>
<td>228</td>
<td>53</td>
<td>1.3</td>
</tr>
<tr>
<td>24</td>
<td>0.68</td>
<td>208</td>
<td>47</td>
<td>306</td>
<td>237</td>
<td>5.1</td>
</tr>
<tr>
<td>48</td>
<td>1.077</td>
<td>274</td>
<td>75</td>
<td>254</td>
<td>185</td>
<td>3.7</td>
</tr>
<tr>
<td>72</td>
<td>1.303</td>
<td>379</td>
<td>117</td>
<td>291</td>
<td>201</td>
<td>3.2</td>
</tr>
<tr>
<td>96</td>
<td>0.9</td>
<td>175</td>
<td>111</td>
<td>194</td>
<td>71</td>
<td>1.6</td>
</tr>
<tr>
<td>168</td>
<td>0.616</td>
<td>174</td>
<td>74</td>
<td>283</td>
<td>162</td>
<td>2.4</td>
</tr>
</tbody>
</table>
the present model, the total hemispheric sodium concentration (the brain sodium contents/the brain water contents) was initially low (about 86 mEq/L) and increased up to 137 mEq/L, a value lower than the serum sodium concentration. Assuming that a significant part of the sodium influx is imbibed into the cells, the intracellular, extracellular, or edema fluid can maintain a sodium concentration lower than that in the serum.

Recently, it has been shown that unipolar sodium transport across the BBB takes place by Na,K-ATPase located in the albuminal side of the endothelial membrane. Although the function of the enzyme is not fully elucidated, it may be involved in the exchange of sodium and potassium following cerebral ischemia. On the assumption that the exchange ratio of sodium/potassium is 3:2 in erythrocytes, the participation of the enzyme system may be roughly estimated by the value of \(\Delta Na/\Delta K\) shown in table 3. The \(\Delta Na/\Delta K\) value was a little greater or close to 1.5 in the early stage of ischemia (3, 6, and 12 hours), but suddenly increased at 24 hours and thereafter. Therefore, the role of the Na,K-ATPase located within the BBB may be significant in the early edema, but would become less important in the later development of edema. The above calculation would even overestimate the role of the enzyme system, since a significant portion of AK is lost in the CSF, whereas the \(\Delta Na\) comes mostly from the blood. Excluding the first 12 hours, the major portion of sodium influx is considered to occur through channels other than the Na,K-ATPase system.

The Alteration of BBB Permeability to Sodium in Late Edema

Later than 12 to 24 hours, the increase in the brain water contents became very pronounced and it was accompanied by a massive sodium influx. As stated in the previous section, the active transport of sodium by Na,K-ATPase was considered to play a rather minor role in this sodium influx. The following discussion will be directed towards the possible pathomechanism involved in the sodium and water movement across the BBB in late edema.

The water movement across the BBB has been considered to follow Starling’s principle, according to which, the water influx in early edema or cytotoxic edema has been explained on the basis of an increase in the idiogenic osmotic activity as well as hydrostatic pressure gradients. As stated earlier, the present data within six hours following ischemia conforms to the above thesis. In the later stage of edema, designated as vasogenic edema, a major cause of water influx has been attributed to the accumulation of proteins in the brain. However, it has also been pointed out that the increased interstitial protein may not elevate tissue osmolality very much. The present study disclosed a dissociation between the water influx and the increased BBB permeability to albumin. Also, a massive water influx preceded the BBB breakdown to albumin, but it was closely correlated with the sodium influx. Therefore, the mechanism of edema formation at late stages seems to be explained better on the basis of an influx of sodium rather than of proteins.

In this regard, Schrier et al. suggested that the sodium influx may be promoted by a decrease in the sodium concentration of the extracellular fluid. Assuming that reflection coefficient of the BBB to sodium remains normal, however, a decrease in the extracellular sodium concentration will create a great osmotic pressure gradient across the BBB. Subsequently, a movement of water from the brain extracellular compartment to the blood will occur, contrary to the observed phenomenon. Therefore, it is rational to assume that an increase in the BBB permeability to sodium has taken place. Increased permeability to solutes is reflected as an increase in hydraulic conductivity and a fall in the value of the reflection coefficient, both of which effects would be expected to increase the water influx across the BBB. It may be mentioned that the osmotic pressure gradient due to a difference in sodium concentration across the BBB disappears as the BBB acquires permeability to sodium. Subsequently, sodium influx across the BBB will occur as a passive diffusion until Donnan’s equilibrium is reached. The injured brain will thus become a source of edema fluid, the composition of which is similar to plasma ultrafiltrate. The above consideration is apparently at variance with the results of the present study, because the calculated sodium concentration in the edema fluid, namely \(\Delta Na - \Delta K/\Delta H_2O\), was much greater than the sodium serum concentration. As discussed earlier, however, this discrepancy can be explained by the occurrence of a massive intracellular shift of sodium, which is presumably due to disruption of the cellular metabolism following ischemia. The above speculation would be supported by the recent report of Hilal et al. which showed a massive accumulation of sodium in the ischemic focus in MCA-occluded cats, using NMR imaging of tissue sodium.

Thus, the results of the present study would permit the interpretation that an increase in the BBB permeability to sodium occurred 12–48 hours after MCA occlusion, which, together with an antecedent intracellular shift of sodium, caused a massive water and sodium influx. Such a pathomechanism of late edema differs from the classical concept of vasogenic edema in that the major cause of water accumulation is the increased BBB permeability to sodium, rather than to proteins. Further studies are required to clarify the mechanism of the BBB permeability change to sodium following ischemia.

Acknowledgments

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