Ischemia in Normo- and Hyperglycemic Rats: Effects on Brain Water and Electrolytes

David S. Warner, Maj-Lis Smith, and Bo K. Siesjö

Previous investigations have shown that preischemic hyperglycemia worsens cerebral outcome. This study sought to delineate the temporal relations between postischemic brain edema and the development of spontaneous epileptiform activity. Fasted rats were subjected to 10 minutes of forebrain ischemia. One-half of the animals were made hyperglycemic by glucose infusion prior to ischemia. At serial recirculation intervals regional specific gravity and cortical electrolytes were measured. Normoglycemic animals showed a biphasic increase in brain water content that was fully resolved by 96 hours and had no convulsive activities. Hyperglycemic brains, although displaying a slower resolution from an initial transient decrease in specific gravity, also developed an interval with normal water content that persisted at 18 hours postischemia. At 24 hours, an increase in water content occurred and was soon followed by the onset of seizure activity. Cortical electrolyte changes were unremarkable until seizures occurred. Significant increases in total Na⁺, Cl⁻, and Ca²⁺ and a decrease in K⁺ were then seen. We conclude that while the normoglycemic brain is capable of resolving postischemic edema in this model, the hyperglycemic brain develops a delayed secondary increase in water content followed by the onset of seizure activity accompanied by a deterioration of ionic homeostasis. (Stroke 1987;18:464–471)

BRAIN edema, i.e., an increase in tissue volume due to the accumulation of fluid, is believed to significantly influence the outcome in stroke.¹ The pathophysiology of this ischemic edema has been intensely explored in animal experiments.²⁻⁷ Such studies demonstrate that the early swelling, noticeable within the first 30 minutes of vascular occlusion, is due to cellular ("cytotoxic") edema; later, a vasogenic mechanism with extravasation of proteins contributes to fluid accumulation.¹⁻⁸

It is less clear to what extent edema contributes to the brain damage incurred as a result of transient ischemia. Long periods of regional or ischemia (30–60 minutes) are followed by accumulation of water, with electrolyte changes characteristic of cellular edema.⁹⁻¹² Under favorable conditions, though, the edema is transient. Controversy revolves around the question of whether a vasogenic component contributes to yield a secondary increase in tissue water content. Thus, while one group has reported that ischemia as brief as 5 minutes will cause vasogenic edema after a delay of many hours,¹¹ another group has published results demonstrating that transient ischemia of 30 minutes duration does not cause vasogenic edema unless the ischemia gives rise to infarction.¹⁰

The question of whether edema contributes to the final damage resulting from transient ischemia received increased attention when it was shown that preischemic hyperglycemia aggravates damage, and that macro- and microscopic swelling was a conspicuous feature in this aggravation.¹³⁻¹⁶ The question also arose whether the exaggerated extra- and intracellular acidosis in hyperglycemic animals caused edema.¹⁷ In this study, we exploited the fact that while most fasted animals exposed to 10 minutes of ischemia develop only selective neuronal necrosis,¹⁸¹⁹ hyperglycemic animals develop seizures and die in status epilepticus about 1 day after the insult. Accordingly, animals with normal or high plasma glucose concentrations subjected to 10 minutes of ischemia were studied at different postischemic periods, and their brains were analyzed with respect to water and electrolyte contents.

Materials and Methods

Eighty-six fasted male Wistar rats (body weight 305–365 g) of an SPF strain (Mollegaard’s Breeding Center, Copenhagen, Denmark) were used for this experiment. Following anesthetic induction with 3.0% halothane in 30% O₂ and balance N₂O, the rats were endotracheally intubated and connected to a small animal respirator (B. Braun Melsungen AG, West Germany), and the delivered halothane concentration was then reduced to 0.7%. The tail artery was catheterized for monitoring of blood pressure and sampling of blood. Via a ventral neck incision, the common carotid arteries were isolated while preserving the vagus nerves and cervical sympathetic plexuses. The right jugular vein was cannulated with a silicone catheter, allowing induction of hemorrhagic hypotension during ischemia. Muscle paralysis was provided by a 1 mg i.v. bolus of suxamethonium chloride (Celocurin, Vimtrum AB, Stockholm, Sweden) repeated as necessary. Bipolar EEG was recorded from a pair of needle electrodes (Mingograf 34, Elema-Schonander, Stockholm, Sweden) inserted into the temporalis muscle on each side of the head.

Following surgical preparation, the halothane was discontinued and the rat allowed a steady-state period of 30 minutes, with rectal temperature maintained between 36.5 and 37.5 °C, Pao₂ at 90–120 mm Hg, and...
Paco₂ at 35–40 mm Hg. Before the sampling of blood for the first blood gas measurement, heparin (50 IU, Vitrum AB, Stockholm, Sweden) was given i.v. Fast- ing plasma glucose levels were measured with a Beck- man Glucose Analyzer 2 (Beckman Instruments Inc., Fullerton, Calif.).

The animals were then randomly assigned to 1 of 2 conditions. One-half (hyperglycemic group) received an i.v. infusion of 25% glucose in Krebs solution (2-3 ml total volume) over a 20-minute period to produce a stable plasma glucose level of 20–25 mmol/l prior to the onset of ischemia. The remaining animals (nor- moglycemic group) received a similar infusion of the vehicle during the same period.

All rats then underwent a 10-minute interval of near- complete forebrain ischemia induced by a bolus i.v. infusion of 2.5 mg trimethaphan camphor sulfate (Arfonad, Roche, Basel, Switzerland) to achieve a mean arterial pressure (MAP) of 50 ± 5 mm Hg, after which both carotid arteries were clamped and a timer started. Central venous exsanguination to maintain MAP at 50 ± 5 mm Hg throughout the ischemic interval was performed as necessary, usually requiring the withdrawal of 5–7 ml of blood. The onset of ischemia was confirmed by an isoelectric EEG. At the end of the 10-minute interval, blood pressure was restored by rapid reinfusion of shed blood, and carotid clamps were removed, the jugular vein tied off, and the neck closed with sutures.

Blood pressure was monitored continuously during the early recovery period. At 15-minute intervals the EEG was recorded and arterial Po₂, Pco₂, and pH were measured. Body temperature was kept near 37° C. After a recovery period of 30–45 minutes, the animals had regained consciousness, resumed spontaneous respira- tion, and could be disconnected from the respira- tor. The animals subsequently were extubated, and the arterial catheter was removed.

Hyper- and normoglycemic rats were then assigned to 1 of 6 subgroups with the duration of the recircula- tion interval (R) varied prior to analysis of brain specif- ic gravity and electrolytes (R = 1.5, 3, 6, 12, 18, or 24 hours). An additional normoglycemic subgroup was measured at R = 96 hours. In the hyperglycemic group 10 animals were allowed to survive beyond 18 hours. Six of these were killed at approximately R = 24 hours, before the onset of motor seizures, and 4 imme- diately after onset of initial gross motor manifestations of seizure activity.

Ten additional rats (5 normo- and 5 hyperglycemic) were prepared as R = 24 hours sham-operated controls. These rats received the same anesthetic and surgical treatment as the experimental animals, with either 25% glucose (plasma glucose level adjusted to 20–25 mmol/l) or Krebs solution (2 ml) infused i.v. immediately after the surgical procedure. The sham- operated controls did not undergo ischemia and were allowed to awaken. The regional specific gravities and electrolyte contents of those brains were examined 24 hours later. To obtain baseline normal values an addi- tional 10 rats did not undergo surgery or ischemia.

These animals were anesthetized with 3.0% halothane in 30% O₂ and balance N₂O and immediately decap- itated for analysis of normal regional specific gravities and electrolyte contents (decapitated normals).

At the completion of the recirculation interval indi- cated, all other animals were reanesthetized with halothane and decapitated. The brains were rapidly removed from the skull and transferred to an ice-cold plate in a gloved chamber (temperature 15° C, relative humidity 90°). Samples (approximately 100 mg) were taken from the parieto-occipital cortex bilaterally, wrapped in foil, immediately immersed in liquid nitrogen, and then stored at −80° C for eventual analysis of electrolyte concentrations. From the sensori- motor cortex, dorsal hippocampus, and caudoputam en, 25-mg samples were dissected bilaterally. These samples were then introduced into a Percoll (Pharma- cia AB, Uppsala, Sweden) linear density gradient with a sucrose concentration of 0.125 M, which was gener- ated according to the method of Tengvar et al.20,21 The column was calibrated using glass spheres with known densities of 1.0300, 1.0350, 1.0400, 1.0450, and 1.0500 g/cm³ (Scientific Glass, Bloomfield, N.J.). Plotting the height in the column occupied by the spheres vs. their known specific gravity (sp gr) assured linearity of the column and allowed extrapolation of the density of the brain samples from the height in the column they occupied 3 minutes after introduction.

Electrolyte determinations were made as follows:22 Cortical samples were weighed, then dried for 48 hours at 105° C, and reweighed. Electrolytes were extracted by treating the dried ground tissue with 0.75 N HNO₃, at 1 ml/100 mg and mixing the stoppered tubes by frequent inversion for 24 hours. The suspension was centrifuged at 10,000 rpm for 10 minutes, and aliquots of the supernatant fluid (extract) were used for the analyses. Chloride concentration was de- termined by mixing 200 µl of extract with 3 ml 0.1 M HNO₃, 10% CH₃COOH plus 3 drops of gelatine re- agent, and measured by a chloride titrator (American Instruments Co., Silver Springs, Md.). Ca²⁺ (200 µl 9% LaCl₃ + 400 µl NaNO₃), Mg²⁺ (2.5 ml 3% LaCl₃ + 50 µl extract), K⁺ (5 ml 0.1% CeCl₃ + 25 µl extract), and Na⁺ (5 ml 0.3% KCl + 25 µl extract) were measured on an atomic absorption spectrometer (Varian Associates Ltd., Surrey, England). Values are reported as mean ± SEM, mmol/kg dry wt.

Data were initially analyzed by one-way analysis of variance (ANOVA). Dunnett’s test was used to deter- mine differences between decapitated normals and exper- imental subgroups. The Newman-Keuls procedure tested for differences between normo- and hyperglyce- mic groups at each recirculation interval and between hyperglycemic groups with and without seizures at R = 24 hours. Statistical significance was assumed at p<0.05.

Results

Physiologic Values

Physiologic values for each subgroup of rats are given in Table 1. ANOVA failed to reveal a difference
between groups in any parameter except preischemia plasma glucose, which was significantly elevated in the hyperglycemic group (p < 0.001). Within the normo- and hyperglycemic groups, however, no significant differences in plasma glucose were seen. All animals demonstrated normal pre- and postischemia blood gases and arterial pH. Rectal temperature was controlled close to 37.0°C. MAP was adequate both before and after ischemia without differences between groups in any parameter except preischemia plasma glucose levels (11.1 and 11.0 mmol/l).

Density Measurements

Regional specific gravities were determined at varying intervals of recirculation; means ± SEM are presented in Table 2. Decapitated normals without surgery or ischemia provided baseline densities of 1.0443 ± 0.0001 (sensorimotor cortex), 1.0443 ± 0.0001 (caudoputamen), and 1.0431 ± 0.0002 g/cm³ (hippocampus). These values were used for statistical comparison with experimental groups. Four of 5 normoglycemic sham-operated animals gave results consistent with the decapitated normals, while 1 animal in this group had atypical values (cortex, 1.0428; caudoputamen, 1.0424; hippocampus, 1.0425). Similarly, 4 of 5 hyperglycemic shams showed no difference from decapitated normals. In the fifth animal the values were cortex, 1.0428; caudoputamen, 1.0427; and hippocampus, 1.0426.

Individual hemispheric values for the sensorimotor cortex are graphed in Figure 1. In both groups, a biphasic pattern of increased water content was found. At R = 1.5 hours, a significant decrease in specific gravity was seen in the normoglycemic group (p < 0.001). This persisted until at least R = 6 hours, and was then followed by an interval of normal values lasting 12–18 hours. At R = 24 hours, a less severe decrease seemed to occur, but this was again fully resolved by R = 96 hours.

The initial postischemia pattern observed in hyperglycemic animals was similar. Again, the early increase in water content was fully resolved by R = 12 hours and was followed by an interval of normal values. At R = 24 hours, prior to the onset of seizures, 6 animals were studied. A significant (p < 0.01) increase in brain water content had occurred (sp gr = 1.0406 ± 0.0013 g/cm³). This was particularly evident in 6 of the 12 hemispheres evaluated. Four animals developed gross motor seizures at approximately this time and were immediately studied. With the onset of seizures the mean sp gr was further decreased to 1.0379 ± 0.0013 g/cm³, not significantly different from the measurements made before convulsive activity was observed. Within the sensorimotor cortex, when the normo- and hyperglycemic groups were compared by Newman-Keuls analysis at each recirculation interval, significantly lower sp gr occurred at both R = 6 hours and R = 24 hours in those animals with elevated plasma glucose (p < 0.01).

Figure 2 demonstrates individual values for the caudoputamen. Again, an early transient increase in water content was observed in both groups. This appeared to be more readily resolved in the normoglycemic group,
Table 2. Regional Specific Gravity as a Function of Preischemia Plasma Glucose Concentrations and Interval of Postischemia Recirculation

<table>
<thead>
<tr>
<th>Recirculation interval (hours)</th>
<th>Region</th>
<th>Sensorimotor cortex</th>
<th>Caudoputamen</th>
<th>Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td>1.0443 ± .0001</td>
<td>1.0443 ± .0001</td>
<td>1.0431 ± .0002</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>1.5</td>
<td>1.0420 ± .0002*</td>
<td>1.0423 ± .0003*</td>
<td>1.0418 ± .0001*</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.0435 ± .0002*</td>
<td>1.0438 ± .0002</td>
<td>1.0425 ± .0004</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.0436 ± .0002*</td>
<td>1.0436 ± .0001</td>
<td>1.0425 ± .0006</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1.0440 ± .0002</td>
<td>1.0448 ± .0002</td>
<td>1.0435 ± .0002</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>1.0446 ± .0002</td>
<td>1.0451 ± .0003*</td>
<td>1.0436 ± .0003</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>1.0440 ± .0001*</td>
<td>1.0406 ± .0006*</td>
<td>1.0435 ± .0002</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>1.0450 ± .0001</td>
<td>1.0447 ± .0001</td>
<td>1.0435 ± .0002</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1.5</td>
<td>1.0422 ± .0002*</td>
<td>1.0427 ± .0003*</td>
<td>1.0415 ± .0002</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.0427 ± .0003*</td>
<td>1.0430 ± .0003*</td>
<td>1.0422 ± .0003</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1.0421 ± .0003*†</td>
<td>1.0426 ± .0002*</td>
<td>1.0421 ± .0003</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1.0442 ± .0001</td>
<td>1.0444 ± .0001</td>
<td>1.0435 ± .0002</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>1.0443 ± .0001</td>
<td>1.0434 ± .0008</td>
<td>1.0439 ± .0002</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>1.0406 ± .0013*†</td>
<td>1.0389 ± .0010*</td>
<td>1.0419 ± .0003‡</td>
</tr>
<tr>
<td></td>
<td>24 (S)</td>
<td>1.0379 ± .0014*</td>
<td>1.0352 ± .0002*</td>
<td>1.0412 ± .0006*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM g/cm³; n, number of hemispheres evaluated; (S), group evaluated after onset of seizures. *p < 0.01, †p < 0.05 (relative to normal); ‡p < 0.01 (normo- vs. hyperglycemic subgroup).

while the hyperglycemic group showed more variability. At R = 12 hours and R = 18 hours, values had returned to normal. Two samples from the same hyperglycemic animal, however, had markedly decreased densities at R = 18 hours. At R = 24 hours the caudoputamen in both groups showed considerable variability, while mean values indicated a significant recurrence of edema. Convulsing animals more consistently demonstrated edema, and samples from this region were significantly less dense when compared with their 24 hour preseizure counterparts (p<0.05).

The hippocampus showed less sensitivity to postischemia edema in the normoglycemic group compared with the cortex and caudate (Figure 3). Only at R = 1.5 hours was a significant decrease in sp gr measured. Although 1 hemisphere at both R = 3 hours and R =6 hours was clearly less dense, this may correlate with the apparent methodologic variability in measurement of hippocampal densities as seen in the 3 aberrant samples in the decapitated normal group. No secondary decrease in sp gr was seen in the normoglycemic group. In the hyperglycemic group, resolution of the initial phase of edema was prolonged with significant decreases in hippocampal sp gr persistent through R = 6 hours. Furthermore, the hyperglycemic hippocampus remained consistent with both the caudoputamen and sensorimotor cortex with respect to reemergence of increased variability and a significantly decreased mean sp gr at R = 24 hours (p<0.05). Convulsions led to a more significant (p<0.01) edema (sp

Figure 1. Specific gravity values for the sensorimotor cortex in normal (N) and in normo- and hyperglycemic animals at different times of recirculation after 10 minutes of ischemia. 24 + S indicates the group with ongoing seizure activity. Each circle represents an individually measured sample from one hemisphere; mean values are given as bars. Normal values are shown as both individual values (left) and mean ± SEM (right). Differences between control and experimental groups were analyzed using Dunnett's test (p<0.01).
Cortical Electrolytes

Parieto-occipital cortical electrolyte values measured by atomic absorption spectroscopy and chloride ion titration are given in Table 3. Water content by the dry weight method was 79.7% in the decapitated normals, corresponding closely with a value of 79.1% based upon calculations made from the sp gr measurements according to the method of Shigeno et al.25 Dry weight values from decapitated normals taken as baseline concentrations were Na⁺, 213 ± 3; K⁺, 509 ± 6; Ca²⁺, 5.55 ± 0.18; Mg²⁺, 33.3 ± 0.4; and Cl⁻, 151 ± 3 mmol/kg. ANOVA failed to demonstrate a significant change in these ionic concentrations in the normoglycemic animals at any postischemia interval evaluated except Cl⁻, which was elevated to 165 ± 4 mmol/kg at R = 1.5 hours. This corresponded to the interval where brain density was most significantly decreased in the sensorimotor cortex and was accompanied by a nonsignificant increase in the Na⁺ concentration to 230 ± 8 mmol/kg.

In the hyperglycemic group, electrolyte concentrations remained significantly unchanged through 6 hours of recirculation except Cl⁻ at 1.5 hours. At R = 12 hours and R = 18 hours, and in the nonseizuring R = 24 hours subgroups, Mg²⁺ was significantly increased over normals. This effect was not seen in those animals exhibiting gross motor seizures. However, in animals at R = 24 hours with seizure, Na⁺ (333 ± 43 mmol/kg), Cl⁻ (198 ± 19 mmol/kg), and Ca²⁺ (9.48 ± 1.56 mmol/kg) concentrations were significantly increased (p<0.01), while the K⁺ concentration was decreased (p<0.01) to 420 ± 38 mmol/kg (Table 3).

Figure 4 depicts individual hemispheric wet weight ionic concentrations for normal animals and hyperglycemic R = 24 hour animals with and without seizures. A close grouping of values was present for all ions until the onset of seizures, when the variability of ionic concentrations greatly increased. The mean values were significantly altered from controls. As can be seen this can be attributed to the effects from 2 of the 4 animals. Comparison of the values from these animals with their respective density measurements suggested an association between severity of edema and the degree of aberration from normal ionic values.

Discussion

Previous investigations have documented that preischemia feeding or glucose infusion adversely affects postischemia recovery.13,14,16,26-27 If hyperglycemic animals are allowed to survive, neurologic sequelae include brain edema and seizure activity.13,16 The interac-

![Figure 2](http://stroke.ahajournals.org/doi/figure/10.1161/01.STR.18.2.468)

**Figure 2.** Specific gravity measurements in the caudoputamen, showing normal (N) and normo- and hyperglycemic animals at different times of recovery following 10 minutes of ischemia. 24 + S indicates the group with ongoing seizure activity. Each circle represents an individually measured sample from one hemisphere; mean values are given as bars. Normal values are shown as both individual values (left) and mean ± SEM (right). Differences between control and experimental groups were analyzed using Dunnett's test (p<0.05; **p<0.01).

![Figure 3](http://stroke.ahajournals.org/doi/figure/10.1161/01.STR.18.2.468)

**Figure 3.** Specific gravity measurements in the hippocampus, depicting normal (N) and normo- and hyperglycemic animals subjected to 10 minutes of ischemia followed by different times of recirculation. 24 + S indicates the group with ongoing seizure activity. Each circle represents an individually measured sample from one hemisphere; mean values are given as bars. Normal values are shown as both individual values (left) and mean ± SEM (right). Differences between control and experimental groups were analyzed using Dunnett's test (p<0.05; **p<0.01).
Table 3. Cortical Electrolyte Concentrations as a Function of Preischemic Plasma Glucose Concentration and Postischemic Recirculation Interval

<table>
<thead>
<tr>
<th>Recirculation interval (hours)</th>
<th>Normal</th>
<th>Normoglycemia</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na⁺</td>
<td>K⁺</td>
<td>Ca²⁺</td>
</tr>
<tr>
<td>Normal</td>
<td>213±3</td>
<td>509±6</td>
<td>5.55±0.18</td>
</tr>
<tr>
<td>1.5</td>
<td>210±6</td>
<td>496±9</td>
<td>5.44±0.20</td>
</tr>
<tr>
<td>6</td>
<td>210±6</td>
<td>496±9</td>
<td>5.44±0.20</td>
</tr>
<tr>
<td>12</td>
<td>210±6</td>
<td>496±9</td>
<td>5.44±0.20</td>
</tr>
<tr>
<td>18</td>
<td>210±6</td>
<td>496±9</td>
<td>5.44±0.20</td>
</tr>
<tr>
<td>96</td>
<td>219±6</td>
<td>512±4</td>
<td>5.84±0.18</td>
</tr>
</tbody>
</table>

Values are mean ± SEM mmol/kg dry wt; (S), group evaluated after onset of seizures. Mean water content for normal brains determined by the dry weight method was 79.7%.

*p < 0.05, t < 0.01 (relative to normal).

The time-dependent interactions between these two phenomena has not been extensively investigated. The availability of a long-term recovery model following an ischemic insult has provided the opportunity to investigate the time-dependent interactions between developing changes in these features as well as simultaneous measurement of neocortical electrolytes in this study.

**Normoglycemia**

When fasted animals underwent 10 minutes of near-complete forebrain ischemia, a biphasic pattern of brain edema characterized by a decrease in regional specific gravity was observed. The initial transient edema resolved within several hours of recirculation, confirming findings by other investigators. This phase most likely represents the previously described cytotoxic edema, which has been attributed to depletion of intracellular energy stores and ionic disequilibrium that when resolved allows restoration of normal parenchymal water content. In our study ionic equilibrium, with the exception of Cl⁻, was maintained. Since there was a suggestive increase in Na⁺ content as well, it seems likely that the cause of the edema was retention of Na⁺ plus Cl⁻ with osmotically obliged water. The alternative is accumulation of "ideogenic" osmoles, e.g., lactate. We cannot exclude this possibility but wish to note that lactate content normalizes in hypo- and hyperglycemic animals long before edema.
Hyperglycemia

When fasted rats were rendered hyperglycemic prior to ischemia, the initial pattern of edema was similar to normoglycemic counterparts but appeared slightly more severe and required a prolonged resolution. Total ionic concentrations remained normal except for a transient rise in Cl\(^-\) during the initial edema phase. However, a significant increase in cortical Mg\(^{2+}\) emerged and persisted through the edema-free interval. The significance of this is unclear. Similar to the normoglycemic group, at R = 24 hours an increase in brain water content occurred before the onset of seizures, but was soon followed by the onset of epileptogenic events. When these occurred the increase in water content was pronounced.

Parenchymal ionic homeostasis did not change until either very close to or immediately after the onset of motor seizures. A marked alteration in ionic content was then seen with the exception of Mg\(^{2+}\), which returned to normal values. We attribute these changes to a profound and widespread cortical depolarization with exhaustion of intracellular energy stores necessary to maintain osmotic gradients. Ionic shifts secondary to experimental posts ischemia epilepsy are not well characterized in the literature. Siemkowicz and Hansen\(^{33}\) found relatively rapid recovery of extracellular H\(^+\) and Ca\(^{2+}\) activities following 10 minutes of ischemia in normo- and hyperglycemic rats, but did not record activities at later times.

Of particular interest is the significant near doubling of the Ca\(^{2+}\) content after the onset of seizures. Sequestration of Ca\(^{2+}\) by the ischemically injured brain is well documented. Yanagihara and McCall\(^{34}\) found a progressive rise in cortical Ca\(^{2+}\) during 3 hours of recirculation after 3 hours of ischemia. Hossmann et al\(^{35}\) reported Ca\(^{2+}\) accumulation during a recirculation period of 3 hours following 60 minutes of ischemia. Ionized Ca\(^{2+}\), usually only poorly permeable across the blood-brain barrier,\(^{36}\) was markedly increased in our study over only a very short period of time, suggesting again a contemporaneous pathophysiological deterioration of this system with the onset of seizures.

The question arises why pres ischemic hyperglycemia leads to a delayed deterioration of water and ionic homoeostasis in the brain. It has seemed likely that hyperglycemia exaggerates ischemic brain damage by enhancing lactic acidosis during the ischemic insult.\(^{37,38}\) In confirmation of this hypothesis, it has been shown that pres ischemic hyperglycemia exaggerates and prolongs the intra- and extracellular acidosis caused by transient ischemia.\(^{39,40}\) However, since the acidosis in normo- and hyperglycemic animals is resolved within the first 1.5 hours of recirculation, any delayed effect of the hyperglycemia, such as that observed in the present study, must be caused by subtle alterations in membrane function persisting for hours following initiation of recirculation. In fact, these alterations may be only indirectly related to the degree of acidosis during ischemia and more directly related to factors operating during recirculation.

In conclusion: Both normo- and hyperglycemic rats demonstrated a biphasic posts ischemia increase in brain water content with an intermediate interval of normal values. Both groups developed secondary edema approximately 24 hours after the insult. While normoglycemic rats were able to elicit full resolution to normal values, hyperglycemic animals went on to develop epilepsy and a major deterioration of cortical ionic gradients. It seems highly justified that the cellular and molecular causes of this delayed deterioration of membrane function be further explored.

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References


Key Words • brain • ischemia • edema • hyperglycemia • electrolytes
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