Early metabolic alterations in edematous perihematomal brain regions following experimental intracerebral hemorrhage

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Object. The authors previously demonstrated, in a large-animal intracerebral hemorrhage (ICH) model, that markedly edematous (“translucent”) white matter regions (> 10% increases in water contents) containing high levels of clot-derived plasma proteins rapidly develop adjacent to hematomas. The goal of the present study was to determine the concentrations of high-energy phosphate, carbohydrate substrate, and lactate in these and other perihematomal white and gray matter regions during the early hours following experimental ICH.

Methods. The authors infused autologous blood (1.7 ml) into frontal lobe white matter in a physiologically controlled model in pigs (weighing approximately 7 kg each) and froze their brains in situ at 1, 3, 5, or 8 hours postinfusion. Adenosine triphosphate (ATP), phosphocreatine (PCr), glycogen, glucose, lactate, and water contents were then measured in white and gray matter located ipsi- and contralateral to the hematomas, and metabolite concentrations in edematous brain regions were corrected for dilution.

In markedly edematous white matter, glycogen and glucose concentrations increased two- to fivefold compared with control during 8 hours postinfusion. Similarly, PCr levels increased several-fold by 5 hours, whereas, except for a moderate decrease at 1 hour, ATP remained unchanged. Lactate was markedly increased (approximately 20 μmol/g) at all times.

In gyral gray matter overlying the hematoma, water contents and glycogen levels were significantly increased at 5 and 8 hours, whereas lactate levels were increased two- to fourfold at all times.

Conclusions. These results, which demonstrate normal to increased high-energy phosphate and carbohydrate substrate concentrations in edematous perihematomal regions during the early hours following ICH, are qualitatively similar to findings in other brain injury models in which a reduction in metabolic rate develops. Because an energy deficit is not present, lactate accumulation in edematous white matter is not caused by stimulated anaerobic glycolysis. Instead, because glutamate concentrations in the blood entering the brain’s extracellular space during ICH are several-fold higher than normal levels, the authors speculate, on the basis of work reported by Pellerin and Magistretti, that glutamate uptake by astrocytes leads to enhanced aerobic glycolysis and lactate is generated at a rate that exceeds utilization.

KEY WORDS • brain metabolite • edema • intracerebral hemorrhage • white matter • pig

We previously demonstrated, in a large-animal ICH model, that markedly edematous areas rapidly develop in white matter adjacent to intracerebral hematomas.46 These edematous regions contain significant accumulations of clot-derived plasma proteins and appear “translucent” on frozen coronal sections as a result of increases in water content that measure more than 10% (Fig. 1). These translucent areas are hyperintense at 2 hours on T₂-weighted magnetic resonance imaging and resemble the perihematomal edematous regions observed on computerized tomography and magnetic resonance images during the early hours following spontaneous ICH in humans.39,37 In the present study, we tested the hypothesis that high-energy phosphates and carbohydrate substrates would be depleted and lactate concentrations would be increased in

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PONTANEOUS intracerebral hemorrhage (ICH), which affects approximately 37,000 individuals per year in the United States, is associated with an approximately 50% mortality rate.2,17 Additionally, 30 to 40% of ICH survivors are left with moderate-to-severe permanent neurological disabilities.2,6,17,25 At present, the complex events that underlie this dismal outcome following ICH are poorly understood. Potential pathophysiological and pathochemical mechanisms that may be involved include mechanical trauma, mass effect and ischemia, toxicity of blood components, and excitotoxicity.20 A better understanding of the pathogenic mechanisms leading to edema formation and tissue damage following ICH should facilitate the development of therapeutic interventions to improve patient outcome.
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perihematomal brain regions during the early hours following ICH due to mass effect and edema.

To study early brain metabolic alterations that occur after ICH, we used a model of lobar ICH that we developed in the pig. In this model, we directly infuse autologous blood into the subcortical white matter by using techniques described by others which we modified. We used data from clinical studies to simulate closely spontaneous lobar ICH in humans with regard to hematoma size and location, rate of blood accumulation, and injection and intracranial pressures. The pig’s large brain size and well-developed white matter enable large blood volumes to be infused; this makes the model useful for studies of hematoma removal. In the present report, we describe our findings of early (first 1–8 hours) metabolic changes in perihematomal white and gray matter. Preliminary reports of these findings have already been presented.

Materials and Methods

Surgical Preparation of Animals, Physiological Monitoring, and Blood Infusion

All surgical, monitoring, and blood infusion procedures were previously described in detail. Preoperatively, pigs (6–8 kg each) were allowed food and water ad libitum. They were initially anesthetized by an intramuscular injection of ketamine (25–30 mg/kg). Deep surgical levels of anesthesia were achieved by intravenous administration of pentobarbital (35 mg/kg) and maintained throughout the experiment by infusion (10 mg/kg/hour). Aseptic techniques were used during all surgical procedures. The pigs were tracheotomized and mechanically ventilated (supplemental oxygen at 1 L/minute) to maintain arterial blood gases and pH within physiological ranges (Table 1). The femoral arteries were catheterized for continuous blood pressure recording and for blood sampling to measure respiratory gases, pH, and glucose concentrations; the femoral veins were catheterized for infusion of saline and pharmacological agents. The animal’s core temperature was measured with a rectal thermistor probe and was maintained at 38.5 ± 0.5°C. Cerebral tissue pressure was measured using a microtip pressure transducer (model SPR-407; Millar Instruments, Inc., Houston, TX) as previously described. Hematomas were produced in 21 pigs by a 15-minute infusion of autologous blood (1.7 ml) through a 20-gauge sterile plastic catheter into the centrum semiovale of the right frontal pole from an in situ frozen brain, demonstrating the hematoma and perihematomal edema in the subcortical white matter. The asterisk indicates white matter regions adjacent to the hematoma (referred to as “translucent”) that were visibly changed in physical appearance because of marked edema (see Table 2). The arrow indicates white matter regions near hematoma that failed to show visible changes (referred to as “normal appearing”) but were mildly edematous (Table 2) compared with posterior ipsilateral or contralateral subcortical white matter.

Brain Tissue Fixation and Sampling

At 1, 3, and 5 hours (five pigs each), and at 8 hours (six pigs) following intracerebral blood infusion, pig brains were frozen in situ with liquid nitrogen as we have previously described for several large animal species including pigs. The frozen heads were cut using a bandsaw into 5-mm-thick coronal sections. Subcortical and cortical gray matter tissue specimens were sampled in a refrigerated glove box (~20°C) at specific sites identified by their relationship to the hematoma. These sites included: “translucent”

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>1 Hr</th>
<th>3 Hrs</th>
<th>5 Hrs</th>
<th>8 Hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(21 pigs)</td>
<td>(21 pigs)</td>
<td>(16 pigs)</td>
<td>(11 pigs)</td>
<td>(6 pigs)</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>144 ± 5</td>
<td>144 ± 4</td>
<td>140 ± 4</td>
<td>138 ± 6</td>
<td>144 ± 4</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>35.4 ± 0.9</td>
<td>37.7 ± 0.9</td>
<td>36.8 ± 1.3</td>
<td>37 ± 1.2</td>
<td>34 ± 1.1</td>
</tr>
<tr>
<td>arterial pH</td>
<td>7.49 ± 0.01</td>
<td>7.47 ± 0.02</td>
<td>7.49 ± 0.02</td>
<td>7.45 ± 0.01</td>
<td>7.48 ± 0.02</td>
</tr>
<tr>
<td>plasma glucose (mM)</td>
<td>6.7 ± 0.3</td>
<td>6.3 ± 0.2</td>
<td>6 ± 0.2</td>
<td>5.3 ± 0.3♀</td>
<td>6 ± 0.2</td>
</tr>
<tr>
<td>core temperature (°C)</td>
<td>38.2 ± 0.1♀</td>
<td>38.6 ± 0.1</td>
<td>38.5 ± 0.1</td>
<td>38.6 ± 0.1</td>
<td>38.7 ± 0.1</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>92 ± 1</td>
<td>102 ± 2♀</td>
<td>102 ± 2♀</td>
<td>98 ± 3</td>
<td>88 ± 2♀</td>
</tr>
<tr>
<td>∆CTP (mm Hg)</td>
<td>—</td>
<td>3.8 ± 0.5♀</td>
<td>5.5 ± 0.6♀</td>
<td>6.5 ± 1.1♀</td>
<td>4.2 ± 1.6♀</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± standard error of the mean (SEM) of the number of animals given in parentheses. Abbreviations:
∆CTP = change in cerebral tissue pressure from control values; MABP = mean arterial blood pressure; — = not applicable.
♀ p < 0.05 compared with control values.
♀ p < 0.05 compared with values at all other time points.

FIG. 1. Photograph of a representative coronal section near the frontal pole from an in situ frozen brain, demonstrating the hematoma and perihematomal edema in the subcortical white matter.
that is based on the conservation of mass in edematous tissue—

\[
\% \text{H}_2\text{O} = \frac{0.05 \text{ compared with contralateral gray matter values.}}{72.88}
\]

\[
1.12 \pm 0.001 \text{ increases in water contents (compared }\]

\[
\text{A correction factor is then applied to the measured metabolite concentrations in edematous brain regions to correct for dilution as demonstrated previously for metabolites, cerebral blood flow, and glucose utilization by Sutton, et al.}\]

\[
\text{Edema was quantitated by determining the water contents of edematous brain regions are expressed as a percentage of wet weight.}
\]

\[
\text{To determine correction factors for metabolite concentrations in edematous white matter, we used the formula derived by Sutton, et al.,}\]

\[
\text{that is based on the conservation of mass in edematous tissue—}
\]

\[
\text{that is, the weights of solids and water in edematous tissue equal the weights of solids and water in the normal brain plus the weights of solids and water in the plasma fluid accumulating in the white matter.}
\]

\[
\text{Rearrangement of this formula yields an equation in which the percentages of water contents of edematous brain regions are used to calculate the correction factors: Correction Factor = }\%
\]

\[
\text{H}_2\text{O} (\text{plasma}) - \%
\]

\[
\text{H}_2\text{O} (\text{control white matter})/ \%
\]

\[
\text{H}_2\text{O} (\text{plasma}) - \%
\]

\[
\text{H}_2\text{O} (\text{edematous brain}).
\]

\[
\text{The water content of plasma is 92%.} \]

\[
\text{A correction factor is then applied to the measured metabolite concentrations in edematous brain regions to correct for dilution as demonstrated previously for metabolites, cerebral blood flow, and glucose utilization by Sutton, et al.}\]

\[
\text{Statistical Analysis}
\]

\[
\text{Data were analyzed by using a one-way analysis of variance (Statgraphics, Version 2.0; Manugistics, Inc., Rockville, MD). Post hoc comparisons between groups were made by using Duncan’s multiple range test. Differences were considered to be significant at a probability level less than 0.05.}
\]

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Time Following Blood Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Hr (5 pigs)</td>
</tr>
<tr>
<td>white matter</td>
<td></td>
</tr>
<tr>
<td>ipsilateral</td>
<td></td>
</tr>
<tr>
<td>translucent</td>
<td>85.25 ± 1.04‡</td>
</tr>
<tr>
<td>normal appearing</td>
<td>75.17 ± 1.06</td>
</tr>
<tr>
<td>posterior</td>
<td>72.37 ± 0.70</td>
</tr>
<tr>
<td>contralateral</td>
<td>72.98 ± 1.09</td>
</tr>
<tr>
<td>gray matter</td>
<td></td>
</tr>
<tr>
<td>adjacent</td>
<td>81.46 ± 0.70</td>
</tr>
<tr>
<td>contralateral</td>
<td>80.41 ± 0.48</td>
</tr>
</tbody>
</table>

* Values are the percentages of wet weight that are expressed as the mean ± SEM of the number of animals given in parentheses.
† p < 0.001 compared with values of all other white matter regions.
‡ p < 0.05 compared with ipsilateral posterior and corresponding contralateral white matter regions.
§ p < 0.05 compared with contralateral gray matter values.

Results

Physiological parameters at the end of the control period and at the times of brain freezing are presented in Table 1. All arterial blood gases and pH values were within normal ranges for pigs, with no significant differences observed at any postinfusion time point. Core temperatures were similar at all time points following intracerebral blood infusions (all values were slightly but significantly higher than control values). Cerebral tissue pressure remained significantly elevated at 4 to 6 mm Hg throughout the postinfusion period in all animals. Cerebral perfusion pressure, calculated as mean arterial blood pressure (MAP) – CTP, was greater than 80 mm Hg at all postfusion time points.

Hematomas were located in the centrum semiovale and extended into the frontal white matter (Fig. 1). As previously described in detail,46 two white matter regions directly adjoined the hematoma that differed markedly in their physical appearance (Fig. 1) and water contents (Table 2). Translucent white matter showed highly significant (p < 0.001) increases in water contents (compared with all ipsilateral and corresponding contralateral white matter regions). Normal-appearing white matter regions also developed significant increases in water contents compared with all other white matter regions except those described as translucent. In gyral gray matter directly overlying hematomas, water contents were significantly increased (p < 0.05) at 5 and 8 hours following blood infusion compared with corresponding contralateral values.

Regional White Matter Metabolites

Adenosine triphosphate concentrations in translucent white matter following correction for increased water content were not significantly different from control except for a 30% decrease (p < 0.05) at 1 hour following blood infusion (Fig. 2 left). In normal-appearing white matter adjacent to hematomas, ATP concentrations were unchanged at 3 and 5 hours, but were significantly (p <
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Fig. 2. Bar graph depicting ATP (left) and PCr (right) concentrations in white matter regions at 1, 3, 5, and 8 hours following blood infusion. See Fig. 1 legend and Materials and Methods for descriptions of white matter regions. Values indicated by the bars and vertical lines are the means ± standard error of the mean (SEM), respectively, for five animals each at 1, 3, and 5 hours and for six animals at 8 hours postinfusion. Left: *p < 0.05 for either translucent or normal-appearing (normal appear) compared with ipsilateral posterior and contralateral white matter; **p < 0.01 compared with all other white matter regions. Right: *p < 0.001 and **p < 0.01 compared with all other white matter regions; †p < 0.05 compared with all other white matter regions.

TABLE 3
Metabolite concentrations and water contents in white and gray matter in control pigs

<table>
<thead>
<tr>
<th>Variable</th>
<th>White Matter (3 pigs)</th>
<th>Gray Matter (3 pigs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(μmol/g)</td>
<td>(μmol/g)</td>
</tr>
<tr>
<td>glycogen</td>
<td>3.71 ± 0.72</td>
<td>7.87 ± 1.20</td>
</tr>
<tr>
<td>glucose</td>
<td>1.69 ± 0.24</td>
<td>2.48 ± 0.38</td>
</tr>
<tr>
<td>PCr</td>
<td>3.55 ± 0.68</td>
<td>2.69 ± 0.82</td>
</tr>
<tr>
<td>ATP</td>
<td>2.39 ± 0.22</td>
<td>2.40 ± 0.25</td>
</tr>
<tr>
<td>lactate</td>
<td>2.87 ± 0.52</td>
<td>2.32 ± 0.49</td>
</tr>
<tr>
<td>water contents</td>
<td>73.56 ± 1.22</td>
<td>81.04 ± 0.42</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SEM in brain tissue samples from three pigs. White matter samples were obtained from the centrum semiovale and gray matter samples were obtained from tips of gyri from a coronal section at the level of the caudate nucleus.

0.05) reduced at 1 hour (by 35%) and at 8 hours (by 45%, p < 0.01).

Phosphocreatine concentrations in translucent white matter were significantly elevated (p < 0.001–0.01) over all other white matter regions in experimental animals and over control white matter values (Table 3) at 3 and 5 hours following blood infusion (Fig. 2 right). No alterations in PCr were present in other white matter regions between 1 and 8 hours following blood infusion, except for a 35% reduction in normal-appearing white matter at 8 hours.

Glycogen concentrations in perihematomal translucent white matter progressively increased to values exceeding fourfold between 1 and 8 hours following blood infusion (Fig. 3 left). At 3, 5, and 8 hours, glycogen concentrations were significantly increased (p < 0.001–0.01) over those in normal-appearing, ipsilateral and contralateral white matter regions and compared with white matter values in control animals (Table 3). No increases in glycogen concentrations were observed in other white matter regions during the 8 hours following hematoma induction. Glucose concentrations were also significantly increased in translucent white matter compared with other white matter regions at 1, 3, and 8 hours (a strong trend was present at 5 hours) (Fig. 3 right).

Lactate concentrations were markedly increased (approximately 10-fold to approximately 20-fold μmol/g) in translucent white matter over all other regions at all time points (Fig. 4). Lactate concentrations were also significantly increased in normal-appearing white matter, as compared with posterior and contralateral white matter regions.

Gyral Gray Matter Metabolite Concentrations

Adenosine triphosphate concentrations in gyral gray matter directly overlying the hematoma were significant-ly (p < 0.05) reduced by 25% as compared with contralateral ATP levels at 1 hour following blood infusion (Fig. 5 left). Thereafter, although ATP values in adjacent gyral gray matter followed a trend to be slightly lower, no significant differences were observed compared with other gray matter structures. Unlike in white matter, PCr concentrations in ipsilateral gyral gray matter regions were similar to contralateral control values at all time points (Fig. 5 right).

Glycogen concentrations in gyral gray matter directly overlying the hematoma were initially decreased (p < 0.05) compared with contralateral gray matter at 1 hour following blood infusion (Fig. 6 left). However, thereafter glycogen concentrations increased in gyral gray matter similar to that observed in edematous perihematomal white matter. Glycogen concentrations returned to control values by 3 hours and continued to increase to values significantly (p < 0.05) greater than other gray matter values by 5 and 8 hours following blood infusion. No significant

Fig. 3. Bar graphs showing glycogen (left) and glucose (right) concentrations in white matter regions at 1, 3, 5, and 8 hours following blood infusion. See Fig. 1 legend and Materials and Methods for descriptions of white matter regions. Values indicated by the bars and vertical lines are the means ± SEM, respectively, for five animals each at 1, 3, and 5 hours, and for six animals at 8 hours postinfusion. *p < 0.05 and **p < 0.01 compared with all other white matter regions; †p < 0.05 compared with ipsilateral posterior and contralateral white matter.
differences in glucose concentrations were observed between gyral gray matter structures at any time point (Fig. 6 right).

Lactate concentrations in gyral gray matter located directly overlying hematomas, but not in distant regions, were significantly ($p < 0.05$) increased at 1, 3, and 8 hours, with a strong trend at 5 hours (Fig. 7).

**Discussion**

Our present findings demonstrate unchanged to increased high-energy phosphate and carbohydrate substrate concentrations along with increased lactate in perihematomal white and gray matter during the early hours following experimental ICH. These results are unexpected and do not support our hypothesis that the hematoma's mass effect and the presence of early edema lead to reductions in high-energy phosphate and carbohydrate substrate concentrations. Alternate explanations for these results are presented later in this section.

Substantial edema development and metabolic findings similar to ours have been described in other brain injury and tumor models. Sutton and coworkers $^{33,34}$ first demonstrated that reduced ATP and PCr concentrations in markedly edematous brain tissue (14.5% increases in water content) after cold injury were an artifact of dilution. After correcting for edema, their high-energy phosphate values were equal to control, whereas the lactate values were further increased. Similarly, decreased ATP levels that precisely matched increased (11.6%) water contents, and were unchanged from control values when expressed on a dry-weight basis, have been described in edematous white matter adjacent to brain tumors. $^{35,26}$

In the present study, our uncorrected ATP, PCr, glycogen, and glucose values were also artifically low (some values were decreased threefold) in markedly edematous white matter. Correcting for dilution resulted in normal to significantly increased values (Figs. 2 and 3). Thus, in regions of perilesional edema, failure to take into account dilutional effects on metabolite levels could lead to the incorrect conclusion that ischemia is present. These results provide additional support for our previous conclusions that the rapid appearance and high water content of edema adjacent to intracerebral hematomas are not due to energy deficiency, but rather appear to result from the accumulation of clot-derived plasma proteins. $^{36}$
Elevated glycogen and glucose levels have been demonstrated in edematous white matter following ICH. Dringen and Hamprecht reported that serum additions doubled carbohydrate substrate and PCr levels suggest that a reduction in metabolism develops in perihematoma brain regions. Indeed, comparable findings of normal-to-elevated high-energy phosphate and glucose concentrations and reduced glucose utilization, indicative of decreased metabolic rates, have been reported in injured hemispheres following cold lesions, fluid-percussion trauma, and subarachnoid hemorrhage that is possibly due to blood products. In addition, glycogen accumulation that is found in the perihematoma white and gray matter in our model and after a variety of experimental injuries is analogous to that observed under conditions that reduce metabolism, such as hypothermia and anesthesia.

Increases in carbohydrate substrate concentration in tissue following ICH may be due to the perihematoma plasma protein accumulation that we previously described in this model. Elevated glycogen and glucose levels have been described in edematous regions adjacent to brain tumors that contain extravasated plasma proteins and in brain tissue following serum injections. Intraparenchymal plasma proteins may contribute to carbohydrate substrate accumulation through a reduction in metabolism. Indeed, Tildon and Stevenson demonstrated that addition of serum albumin to dissociated brain cell cultures reduced glucose oxidation rates by 80%.

Glycogen accumulation following brain injury occurs in astrocytes, the major glycogen storage and metabolizing cells in the central nervous system. These cells contain glycogen synthetase and phosphorylase that have been colocalized with the markers glial fibrillary acidic protein and S-100 protein. Interestingly, Dringen and Hamprecht demonstrated that serum additions doubled the glycogen concentrations in their astrocytic cultures. Furthermore, similar to its glycogen-raising effect in the periphery, insulin and, in particular, insulin-like growth factor I, increased glycogen levels in cultured astrocytes.

The biochemical mechanisms underlying these increases in glycogen are unknown, but may include reductions in phosphorylase activity, as demonstrated following stab-wound trauma and after experimental ICH in rats. The metabolic basis for the lactate accumulation in edematous white matter and in gray matter directly adjacent to hematomas is also unclear. Diffusion of lactate generated by anaerobic metabolism in red blood cells and tumors has been suggested to contribute to elevated lactate levels in surrounding brain regions. Indeed, we previously reported finding markedly higher lactate levels following blunt head trauma in edematous white matter located near brain contusions as compared with samples from noncontused hemispheres. However, elevated tissue lactate levels are also observed 8 hours after severe fluid-percussion injury in the absence of hemorrhage and after plasma infusions. Also, our hematomal lactate levels are only 5 to 8 μmol/g (data not shown), values that are considerably lower than those present in edematous white matter. Increased brain tissue lactate levels are not due to systemic hypoxia, because our animals are mechanically ventilated, have PaO₂ values greater than 100 mm Hg throughout, fail to show increased blood lactate levels (data not shown), and have ipsilateral but distant and contralateral white and gray matter lactate levels that are equal to control values (Figs. 4 and 7).

It has been suggested that elevated white matter lactate levels in both infusion and cold-injury edema and in collagenase-induced ICH are caused by hypoxia-induced stimulations of glycolysis. This hypoxia is believed to result from edema-induced expansion of the extracellular space that increases the distance of white matter axons and cells from their blood supply. If hypoxia is the basis for elevated lactate levels in edematous white matter in our model, its magnitude may be insufficient to reduce high-energy phosphate levels. This conclusion is also supported by normal high-energy phosphates in edematous white matter following the occurrence of freeze lesions and our findings that brain-tissue lactate levels were not significantly higher after ICH in hyperglycemic animals, an expected result if anaerobic glycolysis was markedly stimulated.

We speculate that increased aerobic glycolysis, which has been described in several tissues including brain, underlies the elevated lactate concentrations in edematous white matter following ICH. This enhanced aerobic glycolysis may not necessarily be due to impaired oxidative metabolism, but may reflect intracellular compartmentalization of glycolytic ATP production and utilization. In vascular smooth muscle, ATP from aerobic glycolysis is used to support membrane ATPase activities, whereas ATP for the contractile apparatus is produced by oxidative metabolism. In hippocampal slices, glycolytic ATP is required for potassium uptake.

This conclusion that aerobic glycolysis may underlie the increase in brain-tissue lactate levels after ICH is
based on recent findings of Pellerin and Magistretti. These researchers demonstrated that glutamate, in addition to its receptor-mediated actions as an excitatory transmitter, increases lactate production by astrocytes. This occurs through electrogenic Na⁺/K⁺-ATPase uptake, which stimulates Na⁺/K⁺-ATPase activity and aerobic glycolysis. The coupling between these events is supported by the demonstration that both glutamate transport inhibitors and ouabain markedly reduce lactate production. Because blood glutamate concentrations are approximately 1000-fold higher than normal extracellular space levels, lactate production following an intracerebral bleed may result from increased glutamate uptake by astrocytes and enhanced aerobic glycolysis. Furthermore, the demonstration by Swanson and coworkers that addition of glutamate to astrocytic cultures leads to an increase in oxygen accumulation and reduced glucose utilization may explain our findings in edematous brain regions. Such reduced metabolic rates may also contribute to lactate accumulation following brain injury as suggested by Buczek, et al.4

Conclusions
We can infer from our results that plasma protein accumulation and/or increased glutamate concentrations, particularly in markedly edematous white matter, may contribute to increased glycogen, glucose, and PCr concentrations, possibly through reductions in metabolic rates. This rate reduction may prevent high-energy phosphate depletion as astrocytes attempt to regulate extracellular glutamate by a transport process that is linked to aerobic glycolysis. The consequence of these metabolic changes in astrocytes may result in lactate accumulation following solid astrocytoma and glioblastoma cells. Further studies are needed to confirm these findings in vivo.

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