Relationship Between Plasma Glucose, Brain Lactate, and Intracellular pH During Cerebral Ischemia in Gerbils

David J. Combs, PhD, Robert J. Dempsey, MD, Mary Maley, BS, David Donaldson, and Charles Smith, MD

The dose-response relation between plasma glucose and brain lactate and the relation of these parameters to intracellular pH during severe cerebral ischemia have not been well characterized over a wide range of plasma glucose levels. Experiments to delineate these relations in the gerbil model of global ischemia were performed by using phosphorus-31 nuclear magnetic resonance spectroscopy to measure intracellular pH and a new method to measure brain lactate. Ischemia increased final brain lactate linearly 4 μmol/g for every 100 mg/dl increase in plasma glucose up to 650 mg/dl (p = 0.0001, r² = 0.9); beyond 650 mg/dl, saturation of the glucose transport-glycolysis system occurred. Plasma glucose correlated better with ischemic intracellular pH than did brain lactate. However, when brain lactate levels are compared with intracellular pH during ischemia, the relation may be threshold rather than linear. A narrow transition zone, during which ischemic intracellular pH decreased precipitously with increasing brain lactate, was observed between 17 and 22 μmol/g; below 17 μmol/g, intracellular pH remained stable at 6.8–6.9, whereas above 22 μmol/g, intracellular pH decreased maximally to about 6.2. The marked decrease in intracellular pH that occurs when brain lactate surpasses 17 μmol/g suggests that this sudden drop in intracellular pH may account for the "lactate threshold" for increased cerebral ischemic damage. (Stroke 1990;21:936–942)

Since the observation by Myers and Yamaguchi that glucose infusion increased brain injury from cardiac arrest, the ability of hyperglycemia to enhance cerebral ischemic damage after transient ischemia has become well accepted. The increased ischemic brain damage in the presence of hyperglycemia is believed to be related to increased production of lactate and to the accompanying increase in tissue acidosis. Hyperglycemia produces substantial increases in brain lactate during ischemia, and treatment with a glycolytic inhibitor can block hyperglycemia-enhanced damage. Measurement of interstitial pH and calculation of intracellular pH (pHᵢ) during cerebral ischemia indicate that increased acidosis accompanies increased tissue lactate.

Nevertheless, hyperglycemia studies are often restricted to comparisons of normoglycemic animals with animals that have been made hyperglycemic by one dose of glucose. The dose-response relation between blood glucose and brain lactate over a wide range of blood glucose levels has not been well described in a model of severe cerebral ischemia. Furthermore, the relation between brain lactate and brain pH, during severe global ischemia has not been well characterized over an extensive range of hyperglycemia. The understanding of such relations is especially important in light of the recent finding that brain pathology may be enhanced more by lactic acidosis than by other types of acidosis.

In these experiments, the relation between plasma glucose, brain lactate, and intracellular pH is described over a wide range of plasma glucose levels during 20 minutes of global ischemia in the Mongolian gerbil. pHᵢ is measured by use of phosphorus-31 nuclear magnetic resonance (31P NMR) spectroscopy, and a new method for measuring brain lactate is introduced and discussed.
Methods

Two series of experiments were performed in this study. The first series examined the relation between varying plasma glucose levels and brain lactate levels in control gerbils (nonischemic group [n=30] and in gerbils subjected to bilateral carotid artery occlusion (ischemic group [n=35]). The second series of experiments was performed in a manner similar to the first, except that all gerbils were subjected to ischemia (n=21) and were monitored for brain pH, with \(^3\)P NMR spectroscopy.

In the first experimental series, 65 male Mongolian gerbils (53±1 g [mean±SEM]) were fasted overnight before all experiments. All gerbils were anesthetized with a combination anesthetic (87 mg/kg ketamine hydrochloride plus 13 mg/kg xylazine i.p.) and supplemented as needed. Both common carotid arteries were isolated by means of a lateral incision, and a suture was placed around each artery for easy manipulation. Gerbils were treated intraperitoneally with 0.003 units/kg insulin, saline, or one of four doses of glucose (0.5, 1, 2, or 4 g/kg). All solutions were made up in 0.9% saline, and a total volume of 15 ml/kg was administered to all gerbils. Thirty minutes after treatment, bilateral carotid artery occlusion with vascular clips was performed on 35 gerbils (ischemic group) and was maintained for 20 minutes. After 20 minutes of ischemia, the anesthetized gerbils were decapitated into liquid nitrogen, and blood was collected from the body trunk. In the 30 remaining nonoccluded gerbils (nonischemic group), decapitation into liquid nitrogen was performed 30 minutes after treatment while the gerbils were still anesthetized. The heads were stored in a freezer at -70°C for later measurement of brain lactate. The heparinized body trunk was centrifuged, and the plasma was tested for blood glucose levels. Body temperature was maintained at 37°-38° C throughout the experiment.

In the second experimental series, 21 male Mongolian gerbils (56±2 g [mean±SEM]) were anesthetized after an overnight fast as in the first experimental series. The common carotid arteries were isolated, and dental floss was looped around each artery. The end of a 2.5-cm-long double-lumened vinyl tube (1.1 mm i.d., 2.5 mm o.d.) was placed next to each carotid artery with one end exiting the gerbil just posterior and inferior to the ear. The tubing was held with cyanoacrylate adhesive applied to the skin of the exit wound. Each end of the dental floss was passed through a tube lumen to form a snare by which ischemia could be produced by application of traction. This snare technique was used to minimize changes in the gerbil's position within the magnetic field. The gerbils were treated with one of the six treatments described for the first experimental series. The gerbils were then placed in the magnetic field for \(^3\)P NMR spectroscopy. Approximately 30 minutes after treatment, ischemia was induced in all 21 gerbils and maintained for 20 minutes. The gerbils were then decapitated into liquid nitrogen as previously described. The heads and the trunk plasma were stored at -70°C until brain lactate and plasma glucose could be measured.

Blood samples from the trunk were centrifuged, and a 100-µl sample of serum was analyzed for glucose by the Seralyzer (Ames Division, Miles Laboratories, Inc., Elkhart, Indiana). The Seralyzer analyzes glucose by use of a colorimetric hexokinase method. The colored end product produced by this method is proportional to the glucose present and is monitored by the Seralyzer reflectance photometer at 630 nm.

Samples (0.211±0.010 g [mean±SEM]) were collected from the frontal regions of the frozen brain at room temperature and then returned to the freezer and maintained at -70°C until analysis. The frozen brain samples were weighed and then immediately homogenized in 4 ml sodium fluoride buffer (1 mg/ml sodium fluoride, 0.021 M KH2PO4, and 0.029 M Na2HPO4·2H2O at pH 7.0) kept on ice. Duplicate 25-µl aliquots of the homogenate were analyzed for lactate concentration by an enzyme electrode method with a lactate electrode in a glucose analyzer (model 23A, Yellow Springs Instrument Co., Yellow Springs, Ohio). By using the glucose analyzer, we were able to calibrate to two decimal places instead of the one decimal place possible with the lactate analyzer (model 23L, Yellow Springs Instrument Co.). The lactate electrode contains a membrane composed of a layer of glutaraldehyde-cross-linked L-lactate oxidase, which catalyzes a reaction between L-lactate and oxygen to produce hydrogen peroxide. Hydrogen peroxide then reacts at the platinum anode and produces a current that is linearly proportional to the concentration of lactate in the sample. The technique will be referred to as the lactate analyzer technique. Known solutions of L(+)-lactic acid (0.25, 0.5, 0.75, 1.0, and 2.0 mM) in the sodium fluoride buffer were tested in duplicate to generate a standard curve from which final concentration of the tissue homogenate was calculated. Calibration of the lactate analyzer was checked between each duplicate sample by using a 5 mM L-lactate standard (YSI 2327, Yellow Springs Instrument Co.) provided for the analyzer and a zero lactate flush buffer (YSI 2357, Yellow Springs Instrument Co.). Assuming that 1 g brain tissue has a volume of 1 ml, the lactate concentrations of the tissue were calculated by using the following equation: tissue lactate (µmol/g)=\([\text{tissue volume}+4 \text{ (ml)}]\text{lactate concentration of homogenate (µmol/ml)}]/\text{tissue weight (g)}.

The lactate analyzer has previously been used to measure tissue lactate in muscle. To test the accuracy of the lactate analyzer, 12 gerbils (10 ischemic and two nonischemic) were treated in a manner similar to the first experimental series to produce varying levels of brain lactate. The anesthetized gerbils were decapitated into liquid nitrogen either just before or after 20 minutes of ischemia. Brain samples were removed as in the previous experimental series and divided into two portions: one for analysis by the lactate analyzer technique and the other for analysis by a more com-
mon enzymatic fluorometric technique. The two methods were compared by simple regression analysis.

For the enzymatic fluorometric technique, each brain sample was ground to a fine powder at $-20^\circ$ C with a mortar and pestle. The ground sample was then added to a preweighed microcentrifuge test tube containing 1.0 ml cold 10% trichloroacetic acid solution and mixed. The tube was then reweighed to calculate tissue weight and then centrifuged at 3,200g (3,750 rpm) for 5 minutes at 4$^\circ$ C (GRP centrifuge, Beckman Instruments, Inc., Palo Alto, California). The supernatant was then neutralized with a 1-ml mixture of tri-n-octylamine and Freon 113 (22:78, vol/vol), vortexed for 2 minutes, spun at 3,000 rpm for 5 minutes at 4$^\circ$ C, and stored at $-70^\circ$ C until assayed. The twelve samples were then analyzed for lactate content using the L-lactate enzymatic fluorometric method as described by Passonneau.13

In vivo $^{31}$P NMR spectra (80 MHz) were obtained using a 4.7-T horizontal, 25.4 cm free-bore magnetic resonance imager/spectrometer (SISCO, Fremont, California). The gerbils were positioned in the middle of the magnetic field, and a four-turn, 1.8-cm-diameter copper wire transmit/receive surface coil was placed over the dorsal skull between the ears with the anterior end at the midline of the eyes. The skin above the dorsal skull was left intact. Previous work in the gerbil indicated that removal of the tissue over the dorsal skull does not alter normal brain phosphorus spectra and that little extracranial contamination of the phosphorus signal occurs (authors’ unpublished observations).

Magnetic field homogeneity was optimized by shimming to less than 60 Hz on the proton resonance (200 MHz) of tissue water. Each accumulated $^{31}$P NMR spectrum (spectral width 10,000 Hz, 10,000 data points, 800 repetitions) was obtained by using a nominal 30$^\circ$ pulse and 500-msec repetition time. Intensity correction for saturation was not applied. Sine bell filtering and line broadening of 5 Hz were used in signal processing. The specific peaks followed in these experiments were inorganic phosphate (P$_i$) and phosphocreatine. Average pH$_i$ was calculated by using the position difference (P$_i$ shift) between the P$_i$ and phosphocreatine peaks according to the equation of Petroff et al$^{14}$:

$$\text{pH}_i = 6.77 + \log[(P_i \text{ shift} - 3.29)/(5.68 - P_i \text{ shift})]$$

$^{31}$P NMR spectra were measured before ischemia and during the final 10 minutes of the 20-minute ischemic episode.

Body temperature was maintained at 37°-38° C (range 36°-38.5° C) inside the magnet by placing the gerbils within a tygon tube coil supplied continuously with warm water (K-Module, Baxter Healthcare Corporation, McGaw Park, Illinois) and by blowing warm air through the magnet’s bore.

The data were analyzed by simple regression analysis with analysis of variance (ANOVA) to test whether or not the slope significantly differed from zero. The slope was considered significantly different from zero if $p \leq 0.05$. All analyses were done on a Macintosh SE computer (Apple Computer, Inc., Cupertino, California) using the StatView 512+ statistical package (BrainPower, Inc., Agoura Hills, California).

Results

Brain lactate levels measured by the lactate analyzer compared quite favorably to levels measured in the same gerbils by the more established enzymatic fluorometric technique (Figure 1). Analysis of variance indicated a highly significant slope ($p=0.0001$) that was close to unity (slope=1.14). The $y$ intercept was quite close to the origin ($-0.59$), and the coefficient of determination ($r^2=0.96$) indicated that the two methods were strong predictors of one another.

A summary of plasma glucose and brain lactate values for each treatment group in the first experimental series is presented in Table 1. All remaining discussion of results will focus on data presented for all individual gerbils. Brain lactate did not vary with changes in plasma glucose in nonischemic gerbils; however, the relation between plasma glucose and brain lactate among ischemic gerbils indicated a saturable system (Figure 2). Although a significant slope was found for plasma glucose versus brain lactate among the ischemic gerbils ($p=0.0001$), the coefficient of determination ($r^2$) was only 0.54 due to a tendency for brain lactate to level off once plasma glucose surpassed 650 mg/dl. Under 650 mg/dl, a very strong linear relation (brain lactate=0.04 plasma...
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Figure 2. Scatterplot showing comparison of plasma glucose versus brain lactate for individual gerbils from the first experimental series. Open dots represent nonischemic gerbils. Filled dots represent ischemic gerbils. The regression for nonischemic gerbils was not significantly different from a zero slope. The sloped portion of the line for ischemic gerbils is drawn to reflect the relation observed between brain lactate and plasma glucose levels ≤650 mg/dL. The plateau portion of the ischemic line was drawn to reflect the authors' interpretation that no further increases in brain lactate occur above plasma glucose levels of 650 mg/dL.

Figure 3. Tracings of phosphorus-31 nuclear magnetic resonance spectra measured before ischemia (bottom tracing) and during ischemia (top tracing) in a gerbil treated with 0.5 g/kg glucose. Plasma glucose was 458 mg/dL, and brain lactate was 20.07 μmol/g at the end of ischemia. Cerebral ischemia caused large reductions in phosphocreatine and adenosine triphosphate peaks, a large increase in the P, peak, and a decrease in brain pH from 7.18 to 6.45. In the overall study, pH could not be calculated during ischemia in three of the 21 gerbils because the phosphocreatine peak decreased until it was not distinguishable from background noise.

Both plasma glucose and brain lactate were examined as predictors of ischemic pH using simple linear regression (Figure 4). The slopes of both straight lines were significantly different from zero. However, on the basis of its better coefficient of determination, plasma glucose was a better predictor of ischemic pH than brain lactate. The equations for these linear regressions are as follows:

$$pH_i = (-7.55 \times 10^{-4}) \text{ plasma glucose} + 6.85$$

$$pH_i = (-0.02) \text{ brain lactate} + 6.89$$

Further examination of the relation between brain lactate and pH suggests that the relatively poor cor-
The technique has many advantages including the ability to measure pH, and to make repeated measurements in the same animal. The $^{31}$P NMR spectroscopy method used in this study is best for measuring pH values between 6 and 8 since it is within this range that linearity of the P$_i$ shift is maintained. This technique is not very sensitive in detecting pH values <6. Therefore, it is possible to miss a very acidic population of cells, such as glial cells, which may be capable of attaining pH levels ≤5.21,22 Although this limitation could account for the leveling off of pH$_i$ at about 6.2 as lactate increased above 22 μmol/g, other investigators have detected pH$_i$ changes as low as 5.5 by using NMR spectroscopy. The threshold for marked decreases in pH$_i$ below 6.8-6.9, as lactate surpassed 17 μmol/g, would not be affected by this potential limitation.

Another problem involved in the use of this $^{31}$P NMR technique is whether or not changes in the intracellular free Mg$^{2+}$ during ischemia could compromise the derivation of pH$_i$ from the P$_i$ shift. Changes in the P$_i$ shift with changes in acidity are not altered by Mg$^{2+}$ concentrations ≤2.5 mM. Intracellular free Mg$^{2+}$ concentration for brain tissue has been estimated at 0.5-1.0 mM. Using $^{31}$P NMR spectra, Brooks and Bachelard recently demonstrated in superfused cerebral tissues that the concentration of free intracellular Mg$^{2+}$ in the brain is 0.33 mM and that severe hypoxia increases its concentration to 0.57 mM. Therefore, it seems unlikely that nonischemic or ischemic pH$_i$ measurements were affected by Mg$^{2+}$ levels in the brain.

The first experimental series revealed a strong linear relation between plasma glucose and brain lactate in ischemic gerbils with plasma glucose levels ≤650 mg/dl. Lactate accumulation during ischemia leveled off with levels of plasma glucose >650 mg/dl. A variety of reasons could account for this plateau in lactate accumulation. Since the $K_M$ for glucose transport to the brain is about 6-9 mM, the system for transporting glucose into the brain may be approaching saturation at blood glucose levels >650 mg/dl (36.1 mM); thus, at these levels, the availability of substrate for glycolysis would be limited. The reduction of cerebral blood flow to the gerbil forebrain may have also limited substrate availability and, therefore, maximal lactate accumulation. Because cerebral blood flow is reduced to near zero in the cerebral cortex and to 30% of control in the basal ganglia in this model, substrate availability for glycolysis is mainly restricted to glucose trapped in the vasculature of the brain, intracellular glucose, and glycogen. In a zero-flow situation, the contribution of intravascularly trapped glucose would be small and would maximally increase tissue lactate by 0.67 μmol/g (assuming cerebral blood volume of 6 ml/100 g) for every 100 mg/dl increase in plasma glucose. This is a minor increase compared with the 4 μmol/g increase actually observed for every 100 mg/dl increase in plasma glucose ≤650 mg/dl. It is clear that much of the increase in brain lactate must come from increased intracellular glucose and glycogen although residual

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**Table 1. Plasma Glucose and Brain Lactate Levels in Nonischemic and Ischemic Gerbils of the First Experimental Series**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Plasma glucose (mg/dl)</th>
<th>Brain lactate (μmol/g)</th>
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<tbody>
<tr>
<td></td>
<td>Nonischemic</td>
<td>Ischemic</td>
</tr>
<tr>
<td>Insulin</td>
<td>50±7</td>
<td>51±4</td>
</tr>
<tr>
<td>Saline</td>
<td>197±16</td>
<td>189±13</td>
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<tr>
<td>Glucose</td>
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Values are mean±SEM; n=5 for all groups except ischemic gerbils receiving 4 g/kg glucose (n=10). Nonischemic, control gerbils not subjected to occlusion; ischemic gerbils subjected to bilateral carotid artery occlusion with vascular clips.

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The simpler and faster lactate analyzer technique proved to be an accurate means of measuring brain lactate. Nonischemic brain lactate levels in the first experimental series (Table 1) are comparable with levels found in previous studies. Normal lactate levels from rat brains frozen in situ are 1-2 μmol/g. Decapitation of gerbils into liquid nitrogen produces brain lactate levels of 1.62 μmol/g. Furthermore, for ischemic and nonischemic gerbils, good agreement was observed between the lactate analyzer technique and a common enzymatic technique (Figure 1).

Nuclear magnetic resonance spectroscopy of phosphorus-containing compounds has been used by a number of investigators to measure brain pH during ischemia. The technique has many advantages including the ability to measure pH, and to make repeated measurements in the same animal. The $^{31}$P NMR spectroscopy method used in this study is best for measuring pH values between 6 and 8 since it is within this range that linearity of the P$_i$ shift is maintained. This technique is not very sensitive in detecting pH values <6. Therefore, it is possible to miss a very acidic population of cells, such as glial cells, which may be capable of attaining pH levels ≤5.21,22 Although this limitation could account for the leveling off of pH$_i$ at about 6.2 as lactate increased above 22 μmol/g, other investigators have detected pH$_i$ changes as low as 5.5 by using NMR spectroscopy. The threshold for marked decreases in pH$_i$ below 6.8-6.9, as lactate surpassed 17 μmol/g, would not be affected by this potential limitation.

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Blood flow may contribute as well. However, even if glucose transport was not saturated and some residual flow existed in the normoglycemic ischemic brain, hyperglycemia might still be self-limiting in generating lactic acid because of the ability of hyperglycemia to reduce regional cerebral blood flow. Duckrow et al have demonstrated that regional cerebral blood flow in the normal brain is reduced approximately 7% per 10 mM increment in plasma glucose ≤60 mM. Although it is clear that increased brain lactate production during ischemia is associated with greater decreases in brain pHi, the relation between these parameters over a wide range of lactic acid levels is not as well characterized. Paschen et al observed a linear relation between brain lactate and brain pH after cardiac arrest. Brain lactate increased from about 3 μmol/g to about 11 μmol/g over the first 40 seconds of cardiac arrest; brain pH decreased from 7.0 to 6.0. Blood glucose was not measured or purposely varied in this study. Although this study suggests that the relation between brain lactate and pHi during ischemia is linear, this study was done only over the first 40 seconds of the ischemic insult. Our study looked at total lactate produced over 20 minutes and compared that with pHi, measured during the second half of the ischemic insult. Because cerebral blood flow is reduced to near zero in the cerebral cortex and to 30% of control in the basal ganglia in this model and because brain lactate is maximum in total ischemia within 2–3 minutes, it is likely that pHi and lactate were stable and relatively constant by 10 minutes into the ischemic insult and not under the state of flux, as in the study of Paschen et al. Another reason for the differences found in the relation between lactate and brain pH could reside in the different methods of measuring pH. Paschen et al measured tissue pH, not pHi, by the umbelliferone technique.

Kraig et al examined lactate accumulation versus extracellular pH after complete ischemia and observed a relation similar to that found in this study. Extracellular pH decreased to about 6.81 in animals with lactate levels <13 μmol/g and to 6.18 in animals with lactate levels >16 μmol/g. Between the narrow range of 13 and 16 μmol/g, intermediate changes in interstitial pH were observed. The changes in pH observed during ischemia in our study were quite similar. Intracellular pH decreased to 6.8–6.9 in brains with lactate levels <17 μmol/g and to about 6.2 in brains with lactate levels >22 μmol/g. Intermediate changes in pHi were observed in brains with tissue lactate levels between 17 and 22 μmol/g. It is not clear why there appears to be a nonlinear relation between brain lactate and pHi. Since pHi does not drop beyond 6.8–6.9 until brain lactate concentration surpasses 17 μmol/g, this lactate level may indicate the point at which hydrogen ion production surpasses intracellular buffering capacity. Although adenosine triphosphate hydrolysis, not lactate production, is the primary source of increased hydrogen ion during anaerobic metabolism, 2 mol hydrogen ion are produced stoichiometrically for every mole of glucose converted to 2 mol lactate. The brain lactate range of transition from small to large pH changes in our study is not much wider than those of Kraig et al; however, the level of brain lactate at which pH begins its marked decrease is higher in our study. This difference in lactate threshold for decreased pH may reflect differences in the model or species that was used or differences (i.e., buffering capacity) in the cellular compartment that was monitored.

It is more difficult to speculate why pHi fails to decrease further as brain lactate surpasses 22 μmol/g. As mentioned earlier, it is possible that limitations of 31P NMR spectroscopy in detecting pH changes below 6 are responsible for this observation. Otherwise, it is difficult to reconcile our observations with those of Kraig et al. Although Kraig et al hypothesize that ion-transport characteristics of astroglia maintain a steady-state extracellular pH of about 6.2 despite very high lactate levels, our data do not reveal an intracellular compartment that would continue to become acidic as extracellular pH is maintained.

The ability of hyperglycemia to increase cerebral ischemic damage is associated with ischemic brain lactate levels >20 μmol/g. Below this lactate level,
increased lactate accumulation is not accompanied by increased cerebral ischemic damage. Therefore, hyperglycemia-enhanced damage could be described as a threshold effect with no increase in ischemic damage occurring until brain lactate accumulation during ischemia surpasses 20 μmol/g. Our data also support the lactate threshold concept for increased ischemic damage since pH decreased as brain lactate increased beyond this level. It is possible that it is these large decreases in brain pH that may be responsible for the increased ischemic damage associated with suprathreshold lactate levels.

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References

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