Lactate Uptake and Metabolism by Brain During Hyperlactatemia and Hypoglycemia

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Abstract

Entry into CSF and consumption by brain of blood-borne lactate (La) was quantified in pentobarbital-anesthetized, normocapnic dogs loaded and infused with NaLa and HLa to hold constant, in arterial blood, both the La concentration at about 8 mM (normal = 1 mM) and the pH at 7.4. In four dogs studied hourly over six hours, the arteriosagittal sinus blood concentration difference (ΔA-V La) was 0.41 ± 0.14 (SE) mM (P < 0.05) and was time independent. CSF La rose slowly over four hours to about 0.6 of blood La while cisternal CSF pH remained nearly constant. Four acetate loaded controls showed no changes of ΔA-V La, CSF La, CSF, or arterial pH. Brain uptake of La was quantitated in eight dogs during insulin-induced hypoglycemia, to minimize possible competition by glucose. Cerebral blood flow (CBF) and ΔA-V for La, glucose, and O2 were determined at 30-minute intervals. CBF and cerebral metabolic rate of O2 (CMRO2) both fell about 17% during two hours of hypoglycemia and returned to control with La loading although blood glucose continued to fall to 1.5 mM. In the two hour La loaded period ΔA-V La was 0.27 ± 0.10 mM (n = 32) and CSF La rose to 0.7 of arterial La without altering CSF pH. CMRO2 averaged 1.61 ± 0.14 μmol/(min-gm brain), of which CMR glucose (X6 to give O2 equivalents) provided 75% or 1.18 ±0.13 μO2 eq/(min-gm). CMR La X 3 was 28% of CMRO2 or 0.45 ± 0.15 μO2 eq/(min-gm). The results suggest that blood-borne La can stoichiometrically replace about one-fourth of the glucose used as brain substrate during hypoglycemia, and probably during normoglycemia. Uptake may be limited by saturation of carriers facilitating passage of La across the blood-brain barrier and into brain cells.

Additional Key Words

cerebral blood flow
cerebrospinal fluid
lactacidemia
glucose
blood-brain barrier

Introduction

The questions addressed by this investigation are whether the brain can continuously metabolize lactate (La) or lactic acid delivered to it in the blood, and what fraction of its substrate need can be met by La under optimum conditions, i.e., high blood La level, low blood sugar level and Pao2 > 100 mm Hg. The problem hinges on the permeability of the “blood-brain barrier” to lactate or lactic acid. The barrier here consists not only of the capillary endothelium, but the walls of the cells in which La is to be metabolized. Several recent experiments1-3 have shown that perhaps as much as 15% of the blood-borne 14C labeled L-lactate crosses from blood to brain in one passage through the brain. This, however, does not establish either penetration into brain cells or net uptake and metabolism. Several reports4-6 cast doubt on the quantitative transport of La into brain by showing that neither brain nor CSF La levels were increased 15 to 40 minutes after intravenous injection of large amounts of sodium lactate. Furthermore, Crone and Sørensen7 were unable to detect brain uptake of labeled La during passage of blood through the brain. Posner and Plum,8 observing small, sometimes “negligible” A-V La differences across the brain when CSF La was greatly elevated in both dogs and patients, concluded that La crosses the blood-brain barrier slowly. These reports conflict both with the labeled La uptake and with other reports showing significant amounts of La moving either out of the brain during hypoxia9-11 or into the brain during hypoglycemia or lactacidemia.10,11 The quantitative aspects of such La movements are important not only to an understanding of brain aerobic and anaerobic pathways, but also to characterization of the role of brain lactic acid metabolism in its own acid base balance, particularly as this relates to the regulation of cerebral microcirculation and the chemical regulation of respiration. If blood-brain barrier La transport is via saturable carriers, they may be rate limiting in either the excretion of anaerobically produced La or the uptake and aerobic metabolism of blood-borne...
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La. Cohen et al. estimated the brain La excretion in hypoxic man (Pao, = 35 torr) to be about 20% of glucose consumption, expressing both in O₂ equivalents. If this amount proved to be a transport-limited maximum, it might be anticipated that lactic acid would accumulate within the brain and contribute to vasodilation and hyperventilation.

Methods

Mongrel dogs (15 to 25 kg body weight) were anesthetized with sodium pentobarbital I.V. in a dose of 30 mg per kilogram plus 5 mg per kilogram-hour, paralyzed with gallamine (102 mg per kilogram-hour), and ventilated via tracheostomy with 40% to 60% O₂ to a constant end-tidal Pco₂ of 40 torr, monitored by an infrared CO₂ analyzer. Polyethylene catheters were placed into a femoral artery (for sampling and blood pressure recording), and both femoral veins for I.V. infusions. Thermostated heaters were used to keep rectal temperature at 37.5 ± 1.0°C.

Cerebral venous blood was sampled by a polyethylene catheter cemented (Eastman Kodak 910) into the superior sagittal sinus through a burr hole with the catheter tip about 2 to 3 cm rostral to the torcula. CSF samples were drawn from a polyethylene catheter similarly cemented into the cisterna magna after exposure of the atlanto-occipital membrane. The dogs were in the supine position.

Blood lactate concentration was elevated by infusing a priming dose of 200 mmole of 1 M NaLA (pH adjusted to 7.3) over a five to ten-minute period, followed by infusion at 200 mmole per hour of either 1 M NaLA or 0.6 M HLA as needed to maintain arterial pH at 7.4. Four control dogs were given 1 M sodium acetate (pH adjusted to 7.3) and 0.6 M acetic acid instead of NaLA and HLA.

Arterial and cerebral venous blood samples were drawn simultaneously. Oxygen content of the blood samples was determined by Klingemaier's method in which Pco₂ is measured after 50-fold anaerobic dilution with oxygen-free carbon monoxide-saturated distilled water. Pco₂, Pco₃, and pH were determined at 37°C in appropriate electrodes.

Blood and CSF lactate concentrations were determined enzymatically by the method of Bergmeyer using 1.0 ml of nonheparinized blood or 0.5 ml CSF transferred immediately into two volumes of ice-cold 6% perchloric acid, determining dilution by weight. Glucose concentration was assayed by the hexokinase/glucose-6-phosphate dehydrogenase method, using 1-ml samples added to NaF solution and deproteinated with Nelson-Somojy's reagent.

CBF was determined by the rate of washout of 133Xe from the brain following injection, through a nonocclusive catheter cemented into the left common carotid artery, of about 0.1 ml saline containing about 0.3 mCi of the isotope. Brain 133Xe activity was determined by external scintillation detection utilizing a 1" X 1½" sodium Nal-thallium activated crystal with an integral photomultiplier unit (Harshaw), and a flat field collimator with a one-half energy angle of 30° (skull-crystal distance of approximately 8 cm). The left temporal and parietal skin and musculature were reflected out of the counting field. The slope of the linear regression of In count rate versus time, d(InXe)/dt, was computed during the first minute of washout, beginning six seconds after peak activity was detected.

CBF = λd × (InXe)/dt, ml/(gm-min), where λ = 1.08, the whole brain to blood partition coefficient for Xenon.

Results

Cerebral arteriovenous lactate concentration differences (ΔA-V La) were determined in four dogs over a one-hour control period and a six-hour lactate loaded period, and in four control dogs loaded with acetate over the same period. At the end of the ten-minute injection of 200 mM of NaLa, arterial La was 16 mM, and ΔA-V La was 2.6 ± 1.4 mM. Figure 1 illustrates the rise of CSF La progressively over six hours to about 6 mM with t½ (time to one-half equilibration with arterial La) of 3.5 hours. The mean ΔA-V La values at each sample period are given in Table 1. ΔA-V La (excluding the ten-minute sample) averaged 0.407 ± 0.145 (n = 24), a difference significant at P < 0.05, with no significant time dependent trend. The controls showed no significant ΔA-V La (mean = -0.05 ± 0.02 mM), and no changes in blood, CSF lactate, or pH. La loaded dogs showed a small fall in CSF pH from the fourth to sixth hours, possibly a result of imperfect control of arterial pH by balancing of the infused NaLA and HLA.

Cerebral consumption of glucose, oxygen and lactate was determined in eight animals over a 4.5-hour period consisting of a one-hour control, a 1.5-hour induction of hypoglycemia by I.V. injection of 800 to 1,600 U of bovine regular insulin, and a two-hour La loaded period. Samples were drawn at 30-
TABLE 1
Brain A-V Lactate (La) in Four Lactate and Four Acetate (AC) Loaded Dogs*

<table>
<thead>
<tr>
<th>Loading time, min</th>
<th>Lactate</th>
<th>Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>-60</td>
<td>0.00 ± 0.01</td>
<td>0.28 ± 0.16</td>
</tr>
<tr>
<td>-30</td>
<td>0.02 ± 0.02</td>
<td>-0.04 ± 0.05</td>
</tr>
<tr>
<td>10</td>
<td>2.60 ± 1.37</td>
<td>-0.07 ± 0.10</td>
</tr>
<tr>
<td>60</td>
<td>0.53 ± 0.45</td>
<td>-0.09 ± 0.05</td>
</tr>
<tr>
<td>120</td>
<td>0.49 ± 0.37</td>
<td>-0.02 ± 0.01</td>
</tr>
<tr>
<td>180</td>
<td>0.34 ± 0.42</td>
<td>-0.02 ± 0.02</td>
</tr>
<tr>
<td>240</td>
<td>0.51 ± 0.30</td>
<td>-0.05 ± 0.03</td>
</tr>
<tr>
<td>300</td>
<td>0.31 ± 0.12</td>
<td>0.02 ± 0.08</td>
</tr>
<tr>
<td>360</td>
<td>0.28 ± 0.56</td>
<td>-0.13 ± 0.07</td>
</tr>
</tbody>
</table>

*Continuous infusion of 1 M NaLa and 0.6 M La or 1 M NaAC and 0.6 M acetic acid at 200 mmole per hour for six hours.

minute intervals. Blood glucose fell from about 4.5 mM to 1 to 2 mM as shown in figure 2.

La loading held arterial La at about 7 to 8 mM, and CSF La rose over the two-hour loaded period to about 5 mM, with time of about two hours to reach half the arterial level.

During the last hour of hypoglycemia, CBF and cerebral metabolic rate of O2 (CMRO2) each averaged 17% (P < 0.05) below the mean of the last hour of the control period. Table 2 presents the mean of measured CBF, ΔA-V for La and glucose and the calculated CMR for La, O2, and glucose for the three periods. Excluding the sample ten minutes after beginning the loading in La loaded dogs, the mean ΔA-V La was 0.27 ± 0.10, which was not significantly different from the ΔA-V La in the La loaded normoglycemic dogs studied over six hours. La loading restored CBF and CMRO2 to control levels, of 48 ml per 100 g/min and 1.6 μmol per g-min, respectively, while mean CMR glucose was 1.18 ± 0.13 μO2eq per g-min, and CMR La was 0.45 ± 0.15 μO2eq per g-min (data having been multiplied by six and three, respectively, to obtain O2 equivalent quantities). No significant changes of arterial or CSF pH, PaCO2, PaO2, body temperature, or mean arterial blood pressure were observed. The CMR glucose was not significantly different from CMRO2 during the control and hypoglycemic periods, and no significant uptake or elimination of La occurred during these periods (table 2). The CMR glucose and CMR La represented 75% and 28% of CMRO2, respectively, during the lactate loaded period. The mean influx of La was 0.13 μmol of La, or 0.45 μO2eq per g-min, although the sample taken at ten minutes after beginning the loading showed an influx of about twice this amount at a time when arterial La concentration averaged 14 mM.

Discussion
Brain consumption of blood-borne La averaged 4% to 5% of the arterial lactate entering the brain over six hours without hypoglycemia, and over two hours with hypoglycemia. Hypoglycemia failed to increase this fractional extraction. The La uptake induced by La loading during hypoglycemia was sufficient to restore O2 consumption and CBF to control levels, and the stoichiometric sum of glucose and lactate uptake was not significantly different from the O2 consumed. There appeared to be no progressive decrease of ΔA-V La in either group of animals to suggest that the ΔA-V La was due to saturation of brain tissue with La. The observed La uptake would raise brain lactate concentration 8 mM per hour if none were consumed. If the whole brain La concentration rose at the rate seen in CSF, about 1 to 2 mM per hour, 12% to 25% of observed CMR La could have been stored rather than metabolized. The data are not sufficiently precise to detect such a discrepancy.

In both groups of animals, the ΔA-V La was significantly higher at the end of the initial ten minute loading period when arterial La was 14 to 16 mM. While this increased initial uptake may be mostly stored rather than metabolized, the data nevertheless indicate that the flux of lactate is concentration dependent. This is more consistent with transmembrane diffusion than with a saturable carrier. A major portion of this influx could be accounted for by saturation...
of brain ECF or more permeable, but less metabolically active, cells such as glia. This conjecture is supported by the data at the ten-minute point: glucose and O₂ consumption were equal (within 10%) at 1.1 μO₂eq per gm-min and were 23% below control. At the same time, the La uptake by the brain was 0.70 μO₂eq per gm-min, the excess uptake probably not yet having penetrated into the highly metabolically active brain cells.

La entering CSF may do so either through choroid plexus or by diffusion from brain ECF. Both barriers are sufficiently impermeable that the CSF La rose too slowly to be observed before one hour, as had been noted by both Alexander et al.¹ and Leusen et al.² Klein and Olsen³ found no elevation of brain La 40 minutes after loading blood with La. This does not imply low permeability unless it is established that entering La is not metabolized. Brain ECF is in the diffusion pathway between blood and brain cells, and may be presumed to have an La concentration between arterial and brain cell La. The steady uptake and metabolism of La by brain from one to six hours suggests that brain cell level is not gradually rising, and probably means that La entering the cells is metabolized without a progressive rise in intracellular La. The inference is that brain ECF La also had stabilized within one hour of La loading, and the gradual rise of CSF La was due to the slow exchange of the pool of ventricular or cisternal fluid with both brain ECF and newly formed CSF. The exchange of La between CSF and brain was studied by Prockop⁴ in a ventricular-cisternal perfusion system. He demonstrated a relatively slow efflux from CSF by comparison with a non-metabolized glucose analog, 3-O-methyl D-glucose which utilizes the glucose facilitated transfer, but rapid in comparison with insulin. He concluded that La removal was not via a facilitated transport, although he did not test other weak acids.

The rate of penetration of weak acids and other materials into CSF from blood has been investigated by Rall et al.⁷ In dogs, sulfadiazine, a weak acid, exhibits a half time of equilibration with CSF of about one hour, with a final concentration of 0.8 of plasma concentration due to the somewhat lower pH in CSF. A similar ratio would be expected for La. In the normoglycemic dogs our final ratio was 0.6 for the last three hours, but the blood level was rising slightly over this time, preventing estimation of the steady state CSF/arterial La concentration ratio. The half times estimated for our data relate to the CSF to arterial difference rather than to a final CSF plateau and hence are longer than would apply if we had prolonged the experiment sufficiently to determine the final CSF/arterial La ratio. The more rapid rise of CSF La in the hypoglycemic dogs may be a result of increased frequency and volume of sampling. It is notable that the rising CSF La level did not reduce CSF pH, suggesting that the entering species may not have been HLa, whereas the species undergoing metabolism in cells is HLa. CSF may be misleading as an index of brain cellular or ECF La concentration, although, as pointed out by Posner and Plum, it is a far better index than cerebral venous blood when brain and CSF lactate are elevated above blood levels.

Ashford and Holmes⁸ determined the oxidation

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**TABLE 2**

*Brain-Blood Flow, Oxygen, Glucose and Lactate Metabolism During Insulin-Induced Hypoglycemia* I.V. Lactate Infusion† in Eight Dogs

<table>
<thead>
<tr>
<th>Condition</th>
<th>CSF</th>
<th>A-V</th>
<th>CMR, μO₂eq per gm-min</th>
<th>O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>60.7 ± 6.3</td>
<td>0.03 ± 0.02</td>
<td>0.05 ± 0.04</td>
<td>2.76 ± 0.46</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>45.8 ± 3.5</td>
<td>0.02 ± 0.03</td>
<td>0.03 ± 0.05</td>
<td>1.61 ± 0.31</td>
</tr>
<tr>
<td>La loading</td>
<td>44.8 ± 4.1</td>
<td>0.04 ± 0.03</td>
<td>0.05 ± 0.04</td>
<td>1.36 ± 0.28</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>44.5 ± 2.9</td>
<td>0.01 ± 0.02</td>
<td>0.01 ± 0.03</td>
<td>1.49 ± 0.21</td>
</tr>
</tbody>
</table>

*800 to 1,600 U bovine regular insulin I.V.
†Bolus of 200 mmole I M NaLa (pH = 7.3) followed by continuous infusion of 1 M NaLa or 0.6 M HLa at a rate of 200 mmole per hour.
‡Not included in mean.
torr. Six normoxic dogs studied hourly over six hours.

We have found, as has Oldendorf, that the threefold
metabolism of D-La in brain, while occurring, is
slower than that of L-La. The present results therefore
fail to measure the total La metabolism by brain.

The accuracy of analysis of CMR La is primarily
limited by determination of the difference between
arterial and venous La concentrations, which averaged
about 3% to 5% of the arterial level, a problem which
is intensified by loading to high blood levels. The mean
AA-V La of eight animals was not significantly
different from zero at P = 0.05 at any one time of
sampling except at the end of the ten-minute loading period.
The mean AA-V La of the entire loaded period
was significantly different from zero in both normoglycemia and hypoglycemia.

References
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