Effect of hypoglycemia on postischemic cortical blood flow, hypercapnic reactivity, and interstitial adenosine concentration

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Hypoglycemia increases the vulnerability of the perinatal brain to asphyxia, but it is not known if hypoglycemia-induced changes in cerebral hemodynamics and vascular reactivity underlie this vulnerability. This study tested the hypothesis that hypoglycemia exacerbates postischemic hypoperfusion, and impairs postischemic CO₂ reactivity. The authors also examined the hypothesis that postischemic hypoperfusion is associated with a reduction in the interstitial concentration of the vasodilator metabolite adenosine. Global cerebral ischemia of 10 minutes duration was induced in newborn pigs anesthetized with isoflurane by occlusion of subclavian and brachiocephalic arteries; cortical cerebral blood flow (CBF) and interstitial adenosine concentration were evaluated simultaneously using the combined hydrogen clearance/microdialysis technique. Hypoglycemia (blood glucose < 25 mg/dl) was induced by regular insulin (25 IU/kg) administered intravenously 2 hours prior to induction of ischemia. In the eight normoglycemic animals, baseline CBF was 38 ± 4 ml/min/100 gm and baseline adenosine concentration was 1.2 ± 0.1 μM; in the eight hypoglycemic animals, these values were 39% (p < 0.05) and 62% (p < 0.05) greater, respectively, under baseline conditions. At 1 hour of postischemic reperfusion in normoglycemic animals, CBF was reduced 39% relative to the preischemic baseline (p < 0.01), concomitant with a 27% reduction (p < 0.05) in adenosine concentration, suggesting that this lowered concentration may underlie delayed hypoperfusion.

These postischemic reductions in CBF and interstitial adenosine concentration were significantly greater in hypoglycemic animals, with CBF and adenosine concentration reduced 70% (p < 0.001) and 71% (p < 0.01), respectively, relative to baseline. In nine animals preischemic reactivity to hypercapnia was unaffected by hypoglycemia. Postischemic hypercapnic reactivity was retained in the eight normoglycemic animals, but was attenuated 73% (p < 0.05) in hypoglycemic animals. Thus, in the newborn pig, hypoglycemia exacerbates postischemic cortical hypoperfusion and impairs postischemic cerebrovascular reactivity to hypercapnia.

KEY WORDS • ischemia • hypoglycemia • postischemic hypoperfusion • cerebral blood flow • adenosine • CO₂ reactivity • pig

The incidence of perinatal asphyxia and hypoglycemia remains high, and in many instances, asphyxic episodes secondary to cardiopulmonary disorders or birthing complications occur in hypoglycemic neonates. Hypoglycemia can exacerbate hypoxic-ischemic brain injury in neonates, contrary to findings in adults. Also, hypoglycemic ischemia causes greater metabolic derangements than normoglycemic ischemia. Thus, one might predict that ischemia-induced alterations in cerebral blood flow (CBF) and cerebrovascular reactivity would be adversely affected by hypoglycemia. Paradoxically, the postischemic hypoperfusion typically observed in newborn lambs was absent in hypoglycemic animals. This study was undertaken in a piglet model to further characterize the cerebrovascular status of the neonate following hypoglycemic ischemia. Because studies from our laboratory and others have provided data supporting adenosine’s participation in the regulation of neonatal CBF during hypoxia-ischememia and hypoglycemia, we also measured interstitial purine metabolites concomitant with postischemic CBF under normoglycemic and hypoglycemic conditions.

Materials and Methods

Animal Preparation

All experiments were performed on newborn pigs weighing between 1.8 and 2.8 kg that were less than 5 days of age. The study protocol was approved by the Animal Studies Committee at Washington University School of Medicine. Animals were
anesthetized with ketamine hydrochloride (20 mg/kg) administered intramuscularly. A tracheostomy was then performed, and the animals were mechanically ventilated with a mixture of oxygen, room air, and isoflurane (1.5%), using a rodent ventilator.\(^6\) Core body temperature was monitored with a rectal probe and maintained with a heating pad at 39°C ± 0.5°C. Arterial oxygenation and end-tidal CO₂ were monitored continuously.\(^7\) The left femoral artery was cannulated for the measurement of arterial blood pressure\(^5\) and the left femoral vein was prepared for central infusion of 5% dextrose solution mixed with pancuronium (0.15 mg/kg/hr). The right femoral artery was cannulated for determination of arterial blood gases and glucose. A small lateral thoracotomy was made at the left second intercostal space and a silicon band was placed around the subclavian and brachiocephalic arteries just above the aortic arch for later induction of global cerebral ischemia by snare ligature. The animal was placed in a stereotactic frame, and a burr hole was made in the right frontal bone 3 mm lateral to the sagittal suture and 2 mm anterior to the coronal suture for brain microdialysis.

**Microdialysis/Hydrogen Clearance Methodology**

Methodological details of the modified brain microdialysis technique for simultaneous measurements of purine metabolites and local CBF have been described in earlier reports from our laboratory.\(^5,33\) In this study, the location of the platinum wire electrode was modified so that it spiraled around the outside of the dialysis tubing, juxtaposed with the 5-mm length of tubing that was exposed for solute exchange. The 2-cm-long microdialysis probe was implanted perpendicularly 10 to 12 mm deep from the frontal cortical surface of the brain so that the exposed tubing lay in the frontal cortical gray matter; placement was confirmed by dissection at the end of the experiment. The probe was cemented to the bone with dental acrylic.

Local CBF surrounding the probe was measured by hydrogen clearance, as described previously.\(^5,33\) In brief, hydrogen gas was introduced to the piglet in the inspired air (15% to 20%) for 1 to 2 minutes; the amount of inhaled hydrogen was titrated so that oxygen saturation did not drop below 90%. Thereafter, the inspired hydrogen was turned off and the washout of hydrogen from the brain tissue was monitored by the platinum wire electrode around the dialysis probe. Local CBF was calculated online using customized software.\(^5,33\)

**Experimental Protocol**

Dialysate sample collections for baseline data were not initiated until 90 minutes after implantation of the probe, to allow for attainment of a metabolic steady state.\(^6,8\) Animals were randomly divided into a normoglycemic group (NG) containing eight piglets and a hypoglycemic group (HG) containing eight piglets and a hypoglycemic group (HG) containing eight piglets. Starting 30 minutes after implantation, the microdialysis probe was used to simultaneously test the in vitro recovery for adenosine and glucose at molarities resembling that of the brain interstitial space. The percent recovery for adenosine and glucose was 14.1% ± 1.8% and 12.0% ± 1.0%, respectively; the two variables were highly correlated (r = 0.92). Thus, the in vitro glucose recovery measured at room temperature just prior to implantation of each probe was used to calculate the estimated in vivo concentrations of adenosine and other purines measured with that particular probe.

All values are presented as means ± standard error of the means. Physiological and hemodynamic values determined during the last baseline sampling period were used for within-animal comparisons with ischemia and reperfusion values using paired t-tests. Differences between variables in the NG and HG animals were determined with the unpaired t-test; p values less than 0.05 were accepted as indicating statistical significance.

**Results**

**Hemodynamic Data**

The physiological parameters for all animal groups are shown in Table 1. Occasionally, minor differences
in MABP or blood gas variables were noted between animal groups. During ischemia, MABP increased only in HG animals. Hypercapnia was associated with an increase in MABP and a decrease in pH, as expected.

Cerebral Blood Flow and CO₂ Reactivity

Changes in CBF induced by ischemia in the NG and HG animals are summarized in Fig. 1. Prior to ischemia, CBF in eight HG animals (53 ± 5 ml/min/100 gm) was 40% greater (p < 0.05) than that measured in eight NG animals (38 ± 4 ml/min/100 gm). At 10 minutes of posts ischemic reperfusion, CBF was not significantly different from baseline in NG animals, but was significantly lower than baseline (p < 0.05) in the HG animals. At 30 and 50 minutes of reperfusion, significant hypoperfusion was noted in both groups, but the extent of CBF reduction was significantly greater in the HG animal group at both times (p < 0.05).

Hypercapnic reactivity results are shown in Fig. 2. Prior to ischemia, CBF responses to hypercapnia did not differ between the eight NG and the nine HG animals; thus, hypoglycemia did not affect hypercapnic reactivity. Also, 10-minute global cerebral ischemia did not affect hypercapnic reactivity in NG animals at 70 minutes of reperfusion. However, posts ischemic reactivity to hypercapnia was significantly attenuated (p < 0.05) in animals previously rendered hypoglycemic.

Adenosine and Purine Metabolites

Interstitial purine concentrations are shown in Table 2; adenosine data are summarized in Fig. 3. The baseline interstitial adenosine concentration in eight NG animals was 1.2 ± 0.1 μM. Baseline adenosine concentration was 75% higher (2.1 ± 0.3 μM; p < 0.05) in eight HG animals, consistent with our previous observations. During cerebral ischemia, adenosine increased markedly in both animal groups; although ischemic levels tended to be higher in HG animals than in NG animals, this difference was not significant. At 10 minutes of reperfusion, adenosine concentration was still elevated in both groups; at 30 minutes of reperfusion it had returned to baseline levels in the NG group but was 40% lower than baseline in the HG group. At 50 minutes of reperfusion, adenosine was 27% (p < 0.05) and 71% (p < 0.01) lower than respective baseline levels in the NG and HG animals; the level of adenosine concentration in the HG ani-

### TABLE 1

<table>
<thead>
<tr>
<th>Factor†</th>
<th>Baseline</th>
<th>CO₂</th>
<th>Ischemia</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>CO₂</th>
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<td>MABP (mm Hg)</td>
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<td>NG</td>
<td>53.0 ± 1.8</td>
<td>64.6 ± 2.7</td>
<td>73.3 ± 13.5</td>
<td>48.3 ± 6.8</td>
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<td>65.0 ± 3.5</td>
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<td>57.8 ± 1.8</td>
<td>70.1 ± 3.5</td>
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<td>54.8 ± 1.9</td>
<td>69.0 ± 2.3</td>
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<td>HG-CO₂</td>
<td>54.3 ± 1.8</td>
<td>59.6 ± 2.6</td>
<td>93.1 ± 7.7</td>
<td>55.7 ± 2.4</td>
<td>53.8 ± 2.2</td>
<td>54.4 ± 2.3</td>
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<tr>
<td>NG</td>
<td>95.2 ± 11.8</td>
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<td>99.3 ± 10.3</td>
<td>96.8 ± 13.1</td>
<td>98.2 ± 13.4</td>
<td>101.0 ± 17.1</td>
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<td>91.7 ± 10.7</td>
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<td>20.1 ± 4.5</td>
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<td>NG</td>
<td>7.33 ± 0.03</td>
<td>7.16 ± 0.03</td>
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<td>NG</td>
<td>39.3 ± 4.8</td>
<td>71.6 ± 3.6</td>
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<td>69.0 ± 4.3</td>
<td>33.3 ± 4.1</td>
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<td>32.5 ± 0.4</td>
<td>33.2 ± 1.6</td>
<td>69.3 ± 5.0</td>
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<td>NG-CO₂</td>
<td>35.5 ± 1.6</td>
<td>72.7 ± 3.6</td>
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<td>40.3 ± 2.0</td>
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<td>38.1 ± 1.2</td>
<td>66.4 ± 5.6</td>
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<td>HG-CO₂</td>
<td>31.8 ± 1.3</td>
<td>71.1 ± 2.2</td>
<td>33.0 ± 1.4</td>
<td>35.9 ± 1.5</td>
<td>34.4 ± 0.9</td>
<td>32.5 ± 0.9</td>
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<tr>
<td>NG</td>
<td>98.2 ± 3.9</td>
<td>113.4 ± 11.0</td>
<td>90.8 ± 7.1</td>
<td>89.8 ± 3.7</td>
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<td>HG</td>
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<td>122.7 ± 10.8</td>
<td>97.7 ± 9.8</td>
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<td>114.3 ± 12.0</td>
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<td>NG-CO₂</td>
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<td>111.6 ± 8.0</td>
<td>118.4 ± 5.4</td>
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<td>HG-CO₂</td>
<td>114.0 ± 4.9</td>
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<td>116.2 ± 9.6</td>
<td>117.3 ± 7.8</td>
<td>138.1 ± 7.6</td>
</tr>
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</table>

* Data are mean ± standard error of the mean, measured preschmica (baseline), during ischemia, post ischemia (R1 to R3 = consecutive 20 min reperfusion sampling periods); and during steady-state hypercapnia (CO₂ pre- and post ischemia.
† MABP = mean arterial blood pressure; NG = normoglycemic group (eight animals); HG = hypoglycemic group (eight animals), both groups used for cerebral blood flows and interstitial adenosine concentration determinations; NG-CO₂ = normoglycemic group (eight animals); HG-CO₂ = hypoglycemic group (eight animals), both groups used for CO₂ reactivity determinations.
‡ Significantly different (p < 0.05) from baseline in same group.
§ Significantly different (p < 0.05) from normoglycemic group (NG or NG-CO₂) at same time.
mals was significantly lower (p < 0.05) than that measured in NG animals at this time. With respect to other purine metabolites, interstitial inosine levels were significantly elevated (p < 0.05) during ischemia and during 10 and 30 minutes of reperfusion in both NG and HG animals. Significant increases in hypoxanthine and xanthine levels were observed in both groups only during reperfusion. Hypoglycemia did not affect pre- or postischemic concentrations of inosine, hypoxanthine, or xanthine at any time. Hypercapnia, induced pre- or postischemia, was not associated with a change in adenosine or other purine catabolite levels in either NG animals or HG animals.

### TABLE 2

| Table 2: Interstitial purine metabolite concentrations in each animal group* |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Baseline        | Ischemia        | R1              | R2              | R3              |
| **Factor**       | **Baseline**    | **Ischemia**    | **R1**          | **R2**          | **R3**          |
| adenosine (µM)   |                 |                 |                 |                 |                 |
| NG               | 1.18 ± 0.14     | 13.80 ± 2.56†   | 14.24 ± 5.47†   | 1.17 ± 0.29     | 0.86 ± 0.07†    |
| HG               | 2.07 ± 0.34‡    | 19.29 ± 5.54†   | 10.57 ± 3.14†   | 1.24 ± 0.25     | 0.60 ± 0.07†    |
| inosine (µM)     |                 |                 |                 |                 |                 |
| NG               | 4.80 ± 0.59     | 16.31 ± 2.9†    | 30.90 ± 4.95†   | 22.57 ± 6.75†   | 14.14 ± 4.87    |
| HG               | 3.92 ± 0.45     | 13.64 ± 2.3†    | 28.03 ± 4.33†   | 17.62 ± 4.45†   | 6.75 ± 2.00     |
| hypoxanthine (µM)|                 |                 |                 |                 |                 |
| NG               | 36.23 ± 6.52    | 58.56 ± 13.49   | 68.69 ± 8.53†   | 70.83 ± 10.99†  | 60.87 ± 11.41†  |
| HG               | 33.62 ± 5.63    | 55.21 ± 3.55    | 70.37 ± 5.78†   | 72.31 ± 7.21†   | 57.29 ± 8.82†   |
| xanthine (µM)    |                 |                 |                 |                 |                 |
| NG               | 14.79 ± 3.15    | 15.78 ± 3.41    | 14.94 ± 1.93    | 21.75 ± 4.10†   | 24.19 ± 4.73†   |
| HG               | 12.42 ± 1.80    | 11.61 ± 1.94    | 13.27 ± 1.80    | 20.33 ± 2.44†   | 21.36 ± 3.01†   |

* Data are mean ± standard error of the mean, measured preischemia (baseline), during ischemia, and post ischemia (R1 to R3 = consecutive 20-minute reperfusion sampling periods) in eight animals in the normoglycemic group (NG) and eight animals in the hypoglycemic group (HG).
† Significantly different (p < 0.05) from baseline in the same group.
‡ Significantly different (p < 0.05) from the NG at the same time.
relative to the respective concentrations of purine measured during normocapnic conditions just prior to induction of the hypercapnic stimulus.

Discussion

The results of this study in the piglet lead us to the following conclusions. Temporary global cerebral ischemia in normoglycemic piglets is followed by a period of cortical hypoperfusion, and the reduction in CBF is closely correlated to a reduction in adenosine concentration; also, cortical hypercapnic reactivity remains intact following ischemia. Hypoglycemia elevates CBF and adenosine, but it does not impair the hyperemic response to hypercapnia. However, the combination of temporary ischemia and hypoglycemia causes more profound hypoperfusion, further reduces adenosine during reperfusion, and severely attenuates hypercapnic reactivity. Thus, the increased morbidity and mortality in asphyxiated neonates with concomitant hypoglycemia may result, in part, from augmented postischemic hypoperfusion and impairment in cerebrovascular reactivity to physiological stimuli.

Hypoglycemic Ischemia and Cerebral Blood Flow

Clinical and animal studies indicate that a compensatory hyperemia occurs in response to fasting- or insulin-induced hypoglycemia. Consistent with these findings is the observation in the present study that cortical CBF is elevated 2 to 3 hours after induction of hypoglycemia. In conjunction with our previous report of an early increase in CBF (at 30 minutes of hypoglycemia) and a long-lasting dilation of pial arterioles (for 70 minutes of hypoglycemia), these data indicate that moderately severe hypoglycemia results in a sustained cortical hyperemia in the piglet.

A reactive hyperemia at 10 minutes of postischemic reperfusion was not observed, which is consonant with microsphere-based CBF measures in piglet cerebrum and piglet cortex at 10 minutes of reperfusion. Most likely the hyperemia had subsided by this time, because CBF determinations very early in reperfusion have revealed a hyperemic response in piglet and other neonate models. Findings are mixed, however, on the issue of postischemic hypoperfusion in the neonate, even within the same species. In piglets, our finding of a significant cortical hypoperfusion at 40 and 60 minutes of reperfusion agrees with results from some piglet global ischemia models, but disagrees with others. It is difficult to reconcile these findings because of the variety of methods used to induce ischemia (of varying magnitude); different methods used for CBF determinations and their respective regions of measurements; differences in anesthesia, or lack thereof, and regional heterogeneity in the extent of delayed hypoperfusion.

Although hypoglycemic piglets exhibited increased CBF under nons ischemic conditions in the present study, their CBF during reperfusion was lower than that of normoglycemic animals. Because the mechanisms responsible for delayed hypoperfusion are still unknown, it is difficult to elucidate how the diverse

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**Fig. 3.** Bar graph depicting interstitial adenosine concentration preischemia, during ischemia, and at 50 minutes of reperfusion (RP) after global cerebral ischemia in eight normoglycemic (open bars) and eight hypoglycemic (hatched bars) piglets. Single and double asterisks indicate significant difference (p < 0.05 and p < 0.01, respectively) from baseline value in same animal group; number symbol indicates significant difference (p < 0.05) from normoglycemia at same time.

**Fig. 4.** Graph showing significant correlation (r = 0.726) between interstitial adenosine concentration and cerebral blood flow (CBF) determined concomitantly by the combined microdialysis/hydrogen clearance method in the cortex of eight normoglycemic (open and closed circles) and eight hypoglycemic (open and closed squares) piglets before (open circles and squares) and at 50 minutes of reperfusion (closed circles and squares) following global cerebral ischemia. Linear regression data are shown.
effects of hypoglycemia, including changes in neurotransmitter synthesis, release, and metabolism; disruptions of ion homeostasis, pH and redox state; and phospholipid breakdown, with subsequent free-fatty-acid accumulation. Interact with those of ischemia to adversely influence CBF. It is known that ischemia-induced alterations in energy metabolism in the neonate brain are exacerbated by hypoglycemia. In particular adenosine triphosphate, adenosine diphosphate, and phosphocreatine decline more rapidly and to lower levels in hypoglycemic newborn rats exposed to anoxic conditions relative to normoglycemic littermates, and recent 31P magnetic resonance spectroscopic measurements reveal similar findings in piglets rendered ischemic. Results from studies in newborn dogs indicate that these energy metabolite profiles may result from hypoglycemia-induced impairments in anaerobic metabolism during asphyxia. At present, there are no data available to allow us to determine whether the alterations in postischemic hemodynamics we noted are related to these factors or are the consequence of other pathophysiological changes induced by superimposed hypoglycemia and ischemia.

**Hypercapnic Reactivity**

Researchers continue to affirm that hypercapnic reactivity in adults is intact during hypoglycemia, but impaired following ischemia. Our observation of unaltered reactivity during hypoglycemia in the newborn piglet is similar to the situation in adults, but a recent study noted an attenuated hypercapnic reactivity in the cerebrum of hypoglycemic piglets. Results from studies in newborn dogs indicate that these energy metabolite profiles may result from hypoglycemia-induced impairments in anaerobic metabolism during asphyxia. At present, there are no data available to allow us to determine whether the alterations in postischemic hemodynamics we noted are related to these factors or are the consequence of other pathophysiological changes induced by superimposed hypoglycemia and ischemia.

Hypoglycemic Ischemia and Adenosine Concentration

Our present result demonstrating that adenosine is elevated concommitantly with CBF 2 to 3 hours after induction of hypoglycemia extends previous findings from our laboratory, where increases in these variables were measured out to 30 minutes of hypoglycemia. The implication that adenosine may contribute to mediating this compensatory hyperemic response to reduction in glucose supply is discussed at length in that report.

The large increases in interstitial adenosine concentration during ischemia and early reperfusion confirm earlier studies in newborns and adults. In this study, using the combined microdialysis/hydrogen clearance technique, temporally and spatially coincident evidence was obtained demonstrating that a significant reduction in adenosine concentration occurs later in the reperfusion period, accompanied by a reduction in CBF; furthermore, greater reductions in postischemic adenosine concentration occurred in hypoglycemic animals concomitant with more profound hypoperfusion. Although the significant correlation between adenosine concentration and CBF (Fig. 4) provides a possible mechanism for delayed hypoperfusion, direct evidence is needed to support this hypothesis, particularly because adenosine has not traditionally been considered to exert much tonic vasoconstrictor influence on baseline CBF. In addition, the finding that interstitial adenosine levels did not differ from baseline during postischemic hypoperfusion in adult rats is not in agreement with our observation. It may be that the reduction in local CBF and adenosine we measured simply reflects a reduction in local cerebral metabolism, but our lack of CMRO2 measurements and the controversial nature of the data on postischemic CMRO2 in piglets preclude us from confirming this possible explanation at present. There is scattered evidence from adult animal stud-
ies that adenosine may be involved in the mediation of cerebral hypercapnic dilation. In a previous study in piglets, we observed additive vasodilative actions of hypercapnia and 2-chloroadenosine that were consistent with this possibility. However, because no increase in adenosine concentration was measured in the present study during hypercapnia in normoglycemic animals, either before or after ischemia, we now conclude that adenosine does not participate in this response in our model. Evidence that prostanooids are important mediators of the vasodilative response of the newborn cerebral circulation to hypercapnia remains strong.

Conclusions

In summary, postischemic hypoperfusion is augmented and postischemic hypercapnic reactivity is attenuated by pre-existing hypoglycemia in the newborn piglet. Such hemodynamic features could significantly compromise substrate and oxygen delivery and cerebrovascular autoregulation under this condition, and may therefore contribute to the increased morbidity and mortality associated with perinatal hypoglycemic anoxia, first recognized over a half-century ago.

References


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