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The Effect of Chronic Dexamethasone-induced Hyperglycemia and Its Acute Treatment with Insulin on Brain Glucose and Glycogen Concentrations in Rats

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Background: **In the rat model of forebrain ischemia, long-term dexamethasone treatment is reported to cause hyperglycemia and worsen postischemic functional and histologic injury. This effect was assumed to result from glucose enhancement of intraischemic lactic acidosis within the brain. Short-term insulin therapy restored normoglycemia but did not return histologic injury completely to baseline values. Using a nonischemic rat model, the current study attempted to identify a metabolic basis for such outcome data.**

Methods: **Fifty-eight halothane-anesthetized (1.3% inspired) Sprague-Dawley rats were assigned randomly to be administered either no treatment (N = 18) or 2 mg/kg intraperitoneal dexamethasone (N = 40). The latter were administered dexamethasone 3 h before the study only (N = 8) or for 3 h before the study plus daily for 1 day (N = 8), 2 days (N = 8), or 4 days (N = 16). Of the rats treated with dexamethasone for 4 days, one half (N = 8) were administered an insulin-containing saline infusion subsequently to restore normoglycemia short-term. All other rats (N = 50) were administered an infusion of saline without insulin. Plasma glucose was quantified, and brains were excised after in situ freezing. Brain glucose and glycogen concentrations were measured using enzymatic fluorometric analyses.**

Results: **After 4 days of dexamethasone treatment, plasma glucose was 159% greater than in rats administered placebo (*i.e.*, 22.01 ± 4.66 *vs.* 8.51 ± 1.65 μmol/ml; mean ± SD; $P < 0.0001$). Brain glucose concentrations increased parallel to plasma glucose. An insulin infusion for 27 ± 5 min restored normoglycemia but resulted in a brain-to-plasma glucose ratio that was 32% greater than baseline values ($P < 0.01$). Neither dexamethasone nor the combination of dexamethasone plus insulin affected brain glycogen concentrations.**

Conclusions: **In a nonischemic rat model, dexamethasone alone had no independent effect on the brain-to-plasma glucose ratio. However, short-term insulin therapy caused a dysequilibrium between plasma and brain glucose, resulting in an underestimation of brain glucose concentrations when normoglycemia was restored. The dysequilibrium likely was caused by the rapid rate of glucose reduction. The magnitude of the effect may account for the failure of insulin to reverse dexamethasone enhancement of neurologic injury completely in a previous report that used the rat model of forebrain ischemia. (Key words: Antioxidant steroids; cerebral ischemia; cerebral protection; corticosteroids; glucocorticoids; lactic acidosis.)**

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IN a previous report from our laboratory, Wass *et al.*[1] evaluated the effect of long-term dexamethasone treatment on outcome after transient forebrain ischemia in rats. In the study, dexamethasone caused hyperglycemia and exacerbation of postischemic neurologic function and histologic injury. When additional dexamethasone-treated rats were administered an insulin infusion to restore normoglycemia to baseline values immediately before ischemia, the insulin infusion resulted in a functional outcome similar to that of rats that were administered neither dexamethasone nor insulin. However, the combination of dexamethasone plus insulin was associated with histologic injury that was intermediate, between that of dexamethasone-treated and untreated rats.

We attributed the effects of dexamethasone and dexamethasone plus insulin on functional outcome to a glucose-related mechanism.[1] (As reviewed by Wass and Lanier, increases in blood and brain glucose exacerbate intraischemic lactic acidosis and worsen postischemic outcome. Insulin reduces blood and brain glucose and improves outcome in previously hyperglycemic subjects.) However, we were unsure whether the failure of histologic injury to return to baseline values after insulin infusion was the result of a glucose-related mechanism or some other effect (*e.g.*, a direct toxic effect of dexamethasone[3,4]).

The purpose of the current study was to test the hypothesis that the unexpected histologic outcome data in the dexamethasone plus insulin–treated rats of Wass *et al.*[1] could be explained solely on the basis of a glucose-related mechanism. Specifically, we tested the hypothesis that preischemic treatment with dexamethasone or the combination of dexamethasone plus insulin disrupts brain-to-plasma glucose equilibrium such that, at comparable blood glucose concentrations, treated rats have greater concentrations of brain glucose and glycogen than untreated rats. If this hypothesis were correct, the increases in preischemic brain glucose (*i.e.*, in excess of that estimated by directly measuring blood glucose) would provide the needed substrate to contribute to worsened lactic acidosis during ischemia and a worse postischemic outcome. Our hypothesis was tested in a nonischemic, anesthetized rat model. The primary outcome measurement in our study was the brain-to-plasma glucose ratio, a measurement of brain glucose equilibrium.

Methods

This protocol was reviewed and approved by the Institutional Animal Care and Use Committee of the

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Table 1. Systemic Physiologic Variables at Time of Brain Harvesting

Study Group	N	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pH	Hct (%)	MAP (mmHg)
Control	18	150 ± 12	38 ± 1	7.39 ± 0.01	39 ± 2	86 ± 12
Dexamethasone						
3-h	8	152 ± 10	38 ± 1	7.39 ± 0.02	38 ± 2	86 ± 14
1-day	8	154 ± 7	37 ± 1	7.41 ± 0.02*	37 ± 3	89 ± 20
2-day	8	153 ± 11	37 ± 1	7.41 ± 0.02*	38 ± 2	97 ± 17
4-day	8	153 ± 10	38 ± 1	7.41 ± 0.01*	39 ± 2	101 ± 12
Dexamethasone + Insulin						
4-day insulin	8	159 ± 8	38 ± 1	7.40 ± 0.02	39 ± 5	80 ± 12

Data are mean ± SD.

* $P < 0.01$.

Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension; Hct = hematocrit; MAP = mean arterial pressure.

Mayo Foundation, Rochester, Minnesota. Fifty-eight male Sprague-Dawley rats of consistent age were used in the experiments; they weighed 299 ± 19 g (mean ± SD) before study intervention. The rats were not fed for approximately 12 h before the study but had free access to water. On the day of the study, the animals were weighed again and anesthetized in a plexiglas chamber with 4% inspired halothane in oxygen. After tracheotomy, the trachea was intubated with a 14-gauge flexible catheter (Jelco I.V. Catheter; Critikon, Tampa, FL), and the lungs were mechanically ventilated.

Anesthesia was maintained during the preparatory period with 2–2.5% inspired halothane in 50% oxygen (balance nitrogen). The inspired concentration of halothane was monitored using a Rascal II anesthetic gas analyzer (Ohmeda, Salt Lake City, UT). The rats were paralyzed with 0.5 mg intramuscular pancuronium; additional doses of 0.5 mg intravenous pancuronium were administered every 45 min until study completion.

Temperature was monitored with use of both a rectal thermistor and needle thermistors placed beneath the temporalis muscles bilaterally (models 2100 and 4000A; YSI, Yellow Springs, OH). Body temperature was maintained with use of a heating lamp. Lead II electrocardiographic data were monitored continuously with use of needle electrodes and a polygraph (model 78B; Grass Instruments, Quincy, MA), beginning immediately before tracheal intubation.

Polyethylene catheters (PE-50) were inserted into a femoral artery for blood sampling and pressure monitoring and into a femoral vein for fluid infusion. Arterial blood gases and acid–base status were determined by electrodes at 37°C (model 1306; Instrumentation Laboratory, Lexington, MA). Blood and plasma glucose and lactate were measured using YSI model 1500 glucose and lactate analyzers. Whole blood sodium concentrations were measured using an ion-selective electrode (model 1400 BGElectrolytes; Instrumentation Laboratory).

After initial preparation, the rats were positioned prone, and, after midline incision over the cranium, the skin and muscles of the scalp were reflected, and the underlying calvarium was exposed. A plastic funnel was sutured in place over the calvarium, and the exposed tissues were covered with a sheet of Parafilm (American National Can, Chicago, IL) and gauze to prevent heat and moisture loss.[5–8] Continuous bifrontal electroencephalography was performed with use of needle electrodes and a polygraph (model 78B; Grass Instruments). The animal was returned to the supine position, and the head was secured in a stereotactic headframe.

After surgical preparation was completed, halothane was decreased to 1.3% inspired.[6,7] A 15-min stabilization period followed, after which arterial blood gases, blood glucose, mean arterial pressure, temperature, and inspired halothane concentration were measured and recorded. Appropriate adjustments were made, and additional 10-min stabilization periods were allowed as needed until protocol criteria were met: arterial oxygen tension, 150 ± 25 mmHg (target ± range); arterial carbon dioxide tension, 38 ± 2 mmHg; base excess, 0 ± 2 mEq/l; temperature, 37 ± 0.2°C; and mean arterial pressure greater than or equal to 60 mmHg. If mean arterial pressure was less than 60 mmHg, treatments of 0.5–1 ml intravenous saline, 0.9%, were administered. Bicarbonate was administered as needed in 0.2-mEq doses to maintain adequate base excess.

Rats were assigned randomly to one of six study groups based on the duration of steroid treatment and the type of fluid infusion before brain freezing. Control rats (N = 18) were administered no previous steroid treatment, and their brains were frozen *in situ* after an infusion of 0.9% saline at a rate of 0.75 ml/h for 30 min. The remaining 40 rats were administered dexamethasone in doses of 2 mg/kg intraperitoneally.[1,9] One group underwent short-term dexamethasone treatment (3-hour group; N = 8) and was administered dexamethasone 3 h before brain freezing. Groups undergoing long-term dexamethasone treatment also were administered dexamethasone 3 h before brain freezing but additionally were administered daily intraperitoneal injections of dexamethasone for either 1 day (1-day group; N = 8), 2 days (2-day group; N = 8), or 4 days (4-day group;

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Cranial Temperature (°C)	Glucose		Plasma Lactate (μmol/ml)	Na^+ (mmol/l)	Body Weight (g)
	Blood (mg/dl)	Plasma (μmol/ml)			
37.0 ± 0.1	88 ± 19	8.51 ± 1.65	1.6 ± 0.5	139 ± 1	298 ± 15
37.0 ± 0.1	121 ± 22	11.23 ± 2.15	1.1 ± 0.3	139 ± 2	285 ± 14
37.0 ± 0.1	152 ± 40*	14.37 ± 3.54*	2.4 ± 0.9*	137 ± 2	281 ± 21
37.0 ± 0.1	222 ± 48*	20.99 ± 5.08*	2.6 ± 0.8*	135 ± 1	263 ± 6
37.0 ± 0.1	236 ± 59*	22.01 ± 4.66*	2.8 ± 0.7*	136 ± 3	255 ± 12
37.0 ± 0.1	90 ± 9	8.63 ± 1.70	3.8 ± 0.7*	138 ± 3	260 ± 18

N = 8). These rats also were administered a 30-min intravenous saline infusion immediately before brain freezing. The sixth group (4-day insulin group; N = 8) was administered dexamethasone in a manner identical to the 4-day group, but, instead of plain saline infusion, they were administered a short-term infusion of insulin. Specifically, 0.75 U/ml insulin, in saline, was infused intravenously at a rate of 0.75 ml/h to reduce plasma glucose concentrations to values similar to those in control rats.

When the desired study conditions were attained, the brain was frozen *in situ* using a modification of methods described by Ponten *et al.*[10] that were used previously in our laboratory.[5–8] Briefly, after removal of the paraffin and gauze insulation, the brain was frozen by pouring liquid nitrogen into the funnel overlying the calvarium. Concurrently, physiologic variables were recorded, and an arterial blood sample was obtained for chemical analysis. Mechanical ventilation was continued throughout the freezing period. The head was removed with use of a guillotine and immediately submerged in liquid nitrogen. Subsequently, the brain was removed from the head while being bathed with liquid nitrogen. Then, the extracted brain was stored in a −70°C freezer.

The brain was moved later to a refrigerated box (−20°C) in which the venous sinuses and meninges were dissected away, the hemispheres were separated from each other, and the cortex was removed from the remainder of the cerebrum. This yielded approximately 100 mg cortex/hemisphere for subsequent analysis of brain glucose and an additional 100 mg pooled cortex for glycogen analysis. Glucose was extracted chemically from the cortex[11] and measured with use of an enzymatic fluorometric technique originally described by Lowry *et al.*[12] that was used previously by our laboratory.[5–8,13] The pooled brain sample was divided, and one half was incubated with amyloglucosidase (Sigma Chemical Co., St. Louis, MO), which hydrolyzed glycogen stores.[8,13] Glycogen content, expressed in glycosyl units, was estimated as the difference between the glucose concentration of the hydrolyzed and nonhydrolyzed portions of the analysis.[8,13]

Data from treated rats were compared with control data using a one-way analysis of variance and *post hoc* Bonferroni correction of unpaired *t* tests. Given five possible comparisons to the control group, a Bonferroni corrected probability of 0.05/5 (0.01) was considered statistically significant. Sample size, determined before the study, was based on the assumption that the critical variable in our study was the brain-to-plasma glucose ratio. From preliminary data,[6,7] we designed the study to have a power of 86% to detect a 30% change in brain-to-plasma glucose ratio in the treated groups at an α level of 0.01. All data are reported as mean ± SD.

Results

Systemic Variables

All groups were well-matched for systemic physiologic variables, except plasma glucose at completion of surgical preparation (untabulated data) and at the time of brain freezing (table 1).

Effects of Dexamethasone Treatment

In the control group, plasma glucose at the time of brain harvesting was 8.51 ± 1.65 μmol/ml. Dexamethasone resulted in increases in plasma glucose in proportion to the duration of treatment (table 2). Plasma glucose at the time of brain harvesting ranged from 11.23 ± 2.15 μmol/ml in the 3-hour group to 22.01 ± 4.66 μmol/ml in the 4-day group. The latter was an increase of 159% more than control values ($P < 0.0001$).

Brain glucose concentrations also increased in proportion to treatment duration (table 2). In the control group, brain glucose was 2.09 ± 0.45 μmol/g. In dexamethasone-treated groups, brain glucose ranged from 2.65 ± 0.50 μmol/g in the 3-hour group to 5.87 ± 0.85 μmol/g in the 4-day group. The latter was an increase of 181% more than control values ($P < 0.0001$).

The brain-to-plasma glucose ratio was 0.25 ± 0.05 in the control group. Dexamethasone alone had no effect on this ratio (table 2) Brain glycogen was 4.66 ± 1.32 μmol/g in control rats. It was not altered significantly by dexamethasone treatment (table 2).

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Table 2. Brain Concentrations of Glucose and Glycogen, and Brain-to-plasma Glucose Ratios

Study Group	N	Glucose (μmol/g)	Glycogen (μmol/g)	Brain-to-Plasma Glucose Ratio
Control	18	2.09 ± 0.45	4.66 ± 1.32	0.25 ± 0.05
Dexamethasone				
3-h	8	2.65 ± 0.50	4.50 ± 0.70	0.24 ± 0.04
1-day	8	3.64 ± 0.88*	4.65 ± 0.97	0.26 ± 0.04
2-day	8	5.08 ± 0.77*	5.09 ± 0.84	0.25 ± 0.03
4-day	8	5.87 ± 0.85*	5.19 ± 1.14	0.27 ± 0.04
Dexamethasone + Insulin				
4-day insulin	8	2.85 ± 0.88	4.69 ± 0.71	0.33 ± 0.09*

Data are mean ± SD.

* $P < 0.01$.

Effects of Dexamethasone Plus Insulin Treatment

In the dexamethasone plus insulin–treated 4-day group, an insulin infusion for 27 ± 5 min produced a plasma glucose concentration of 8.63 ± 1.70 μmol/ml at the time of brain harvesting. This value was similar to that of the control group (8.51 ± 1.65 μmol/ml). Despite this, there was a tendency for brain glucose concentrations to differ between the 4-day insulin group (2.85 ± 0.88 μmol/g) and the control group (2.09 ± 0.45 μmol/g; $P = 0.012$; table 2).

The combination of dexamethasone plus insulin resulted in significant alterations in the brain-to-plasma glucose ratio. The ratio in 4-day insulin rats (0.33 ± 0.09) was 32% greater than the value in control rats (0.25 ± 0.05; $P < 0.01$; table 2). Brain glycogen concentration in 4-day insulin rats (4.69 ± 0.71 μmol/g) was similar to that in control rats (4.66 ± 1.32 μmol/g; table 2).

Discussion

In the current study, we determined that dexamethasone had no independent effect on brain glucose equilibrium, as shown by the brain-to-plasma glucose ratio (table 2). However, short-term insulin therapy caused dysequilibrium between plasma and brain glucose, resulting in an underestimation of brain glucose concentrations when normoglycemia was restored.

The lack of an independent effect of dexamethasone to increase the brain-to-plasma glucose ratio is consistent with previous research. Other studies have reported that dexamethasone inhibits glucose transport into cultured hippocampal neurons and glia,[14] depresses local glucose use in rats with cortical freezing lesions,[15] and reduces brain glucose uptake in patients with brain tumors.[16] The related steroid compound, hydrocortisone, has no independent effect on brain hexose transport.[17]

In the current study, disruption of brain-to-plasma glucose equilibrium occurred only when dexamethasone-treated rats underwent short-term insulin infusion to reduce blood glucose concentrations rapidly. During these experimental conditions, the ratio was 32% greater than in the control group (table 2). Based on previous research in our model[6–8] (see the following discussion), we speculate that the current observation (table 2) probably was not a direct effect of insulin on the brain but instead represents a state of dysequilibrium related to the rate of blood glucose reduction.

Using the same model as in the current study, Weglinski and Lanier[5] rapidly increased plasma glucose concentration from 10.1 ± 1.1 to 43.8 ± 5.2 μmol/ml using a 30-min-duration glucose infusion.‖ When glucose infusion was discontinued, blood glucose concentrations returned to values that approximated baseline during the ensuing 90 min. This research determined that rapid increases in blood glucose resulted in a 27% reduction in the brain-to-plasma glucose ratio. In contrast, during periods of rapid decrease in brain glucose, there was an increase in the brain-to-plasma glucose ratio by as much as 25%. The largest alteration in the ratio occurred during a period in which plasma glucose concentration decreased from 43.8 ± 5.2 μmol/ml to 22.1 ± 2.2 μmol/ml over 30 min (*i.e.*, a rate of 43.4 $\mu mol \cdot ml^{-1} \cdot h^{-1}$). This increase in the brain-to-plasma glucose ratio is qualitatively similar to the response we observed in the insulin-treated rats in the current study, with plasma glucose decreasing at a rate of 29.7 $\mu mol \cdot ml^{-1} \cdot h^{-1}$ (rate calculated from table 2 data). These large rates of decrease in plasma glucose in both investigations (table 2)[5] bracket the rate of decrease in the outcome study of Wass *et al.*[1] (38.7 $\mu mol \cdot ml^{-1} \cdot h^{-1}$). Therefore, it likely that the methods of Wass *et al.*[1] also resulted in a meaningful increase in the brain-to-plasma glucose ratio.

We suspect that the dysequilibrium between blood and brain glucose concentrations observed in the current study and the potential to generate a similar state of dysequilibrium clinically could be avoided simply by altering the insulin dose and reducing blood glucose concentrations more slowly. This notion is supported by

‖ We estimated plasma glucose concentrations in the Weglinski and Lanier[5] study based on reports of blood glucose concentrations, with use of a formula generated from the raw data of Hofer and Lanier:[7] Plasma glucose in μmol/ml = (blood glucose in mg/dl − 1.9)/11.1. The calculations given are based on the estimated plasma values.

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two separate studies from our laboratory. In anesthetized rats with drug-induced diabetes mellitus, the use of insulin infusion to reduce plasma glucose concentrations by a peak rate of 12 or 13 $\mu mol \cdot ml^{-1} \cdot h^{-1}$ resulted in no significant independent effect of insulin on the brain-to-plasma glucose ratio (*i.e.*, the ratio changed by $<$ 10%).[6,7]

Our conclusion that the effects of insulin on the brain-to-plasma glucose ratio are entirely rate dependent is challenged potentially by the report of Pelligrino *et al.*[18] These authors administered short-term intravenous boluses of insulin to Sprague-Dawley rats that had been made chronically hyperglycemic (for 6–8 weeks) as a result of streptozotocin-induced diabetes. They reported that short-term glucose normalization caused an increase in the brain-to-plasma glucose ratio, which, in turn, was associated with an increase in brain glucose influx that was greater than a concomitantly observed increase in cerebral metabolic rate for glucose. Pilot data from three rats in the model showed that the increased brain-to-plasma glucose ratio persisted even when glucose normalization occurred over 18–24 h. There are several differences between the study of Pelligrino *et al.*[18] and ours that could have led to these differing observations. In contrast to the rats in our current and previous reports[6,7] that were studied during conditions of a surgical plane of anesthesia, Pelligrino *et al.*[18] studied rats that were paralyzed with curare and underwent mechanical ventilation during sedation with 70% nitrous oxide (*i.e.*, approximately 0.35 minimum alveolar concentration in Sprague-Dawley rats[19]). Although plasma glucose concentrations in their untreated nondiabetic and insulin-treated rats were similar to those in our study, the pre-insulin plasma glucose concentrations in their diabetic rats were 50% greater than in our dexamethasone-treated rats. Furthermore, their rats had hyperglycemia for a longer duration (*i.e.*, 6–8 weeks *vs.* 4 days) before insulin infusion. Additionally, the rats of Pelligrino *et al.*[18] were administered a supraclinical insulin dose that was approximately eightfold greater than in our rats (*i.e.*, 8 *vs.* 1 U/kg body weight). These methodologic factors in the study of Pelligrino *et al.*[18] could have had the following effects on physiology. (1) The large dose of insulin could have introduced a mechanism not seen with clinical doses. (2) A longer duration of glucose increase and a larger glucose reduction should have increased the likelihood of hypoglycemic symptoms and the counterregulatory physiologic response observed in chronically hyperglycemic patients after short-term glycemic reductions to the normal range.[18,20,21] Of note, this counterregulatory response is independent of the rate of glucose reduction.[20] (3) Perhaps more importantly, the use of sedation instead of a surgical dose of anesthesia in paralyzed rats undergoing mechanical ventilation would have permitted a physiologic stress response to develop, either independent of drug treatment or as a result of the counterregulatory mechanisms that accompany short-term glycemic normalization.[20,21] Unfortunately, because we measured neither glucose flux nor metabolic rate in our current or previous studies,[6,7] it is not possible to make direct mechanistic comparisons with the study of Pelligrino *et al.*[18] However, because of our previous experience in the surgically anesthetized rat model (*i.e.*, relatively gradual glucose reduction with insulin has no independent effect on brain-to-plasma glucose equilibrium[6,7]), we suspect that the study of Pelligrino *et al.* [18] and our current study (table 2) identified alterations in the brain-to-plasma glucose ratio that originated from differing mechanisms.

It is well-known that, during periods of severe global ischemia, glucose originating as either free glucose or glycogen is metabolized[8,13] and contributes to toxic intracellular lactic acidosis.[2] In the current study, neither dexamethasone nor the combination of dexamethasone plus insulin significantly affected brain glycogen concentrations (table 2).

The significance of these unaltered brain glycogen concentrations and their relation to a survivable cerebral ischemic injury are as follows. During the early phases of ischemia, the brain preferentially metabolizes free brain glucose to supply energy.[8,13,22] A slight temporal delay in the onset of glycogen metabolism probably results because free glucose is more readily available as an energy source and also because glycogen must first be hydrolyzed before it can liberate additional free glucose. Delays in glycogen metabolism are more pronounced in previously hyperglycemic subjects than in normoglycemic subjects, presumably because there are greater concentrations of free brain glucose available. Intraischemic glycogen metabolism continues after brain concentrations of free glucose are exhausted and also continues into the period of reperfusion.[8,13,22] Thus, a meaningful fraction of glycogen metabolism may occur after lactate accumulation (a marker of acidosis) already has surpassed the threshold for irreversible brain injury.[8,13] This is particularly true in hyperglycemic subjects.

When such concepts of ischemic glucose and glycogen metabolism are extrapolated to the current study and the study of Wass *et al.*,[1] it becomes apparent that the brain-to-plasma glucose relation, not the relation of brain glycogen to plasma glucose, is the more important variable in terms of clinical management.

In summary, the current study determined that dexamethasone alone had no effect on net brain glucose equilibrium, as determined by the brain-to-plasma glucose ratio. However, short-term insulin therapy caused dysequilibrium between plasma and brain glucose, resulting in underestimation of brain glucose concentrations when normoglycemia was restored. The dysequilibrium probably was caused by the rapid rate of glucose reduction in our study and was not a direct effect of insulin on the brain. The magnitude of the dysequilib-

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rium may help to explain previous postischemic outcome results in the rat model of forebrain ischemia,[1] and the results may warn of potential problems with rapid glucose alterations in patients at risk for cerebral ischemic injury. We speculate that the dysequilibrium observed in the current study could have been avoided simply by lessening the rate of glucose reduction.

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