Anesthesiology
72:1045–1050, 1990

Brain Lactate and Neurologic Outcome Following Incomplete Ischemia in Fasted, Nonfasted, and Glucose-loaded Rats

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The neurologic outcomes following incomplete cerebral ischemia in rats treated by fasting, nonfasting, or glucose administration (6 ml/kg of 50% glucose solution intraperitoneal) were compared. Rats were anesthetized with 1.4% inspired isoflurane in air and incomplete ischemia was produced by temporary unilateral carotid occlusion and hypotension of 30 mmHg for 30 min. The rats were recovered and neurologic outcome was scored every 8 h for 3 days using a 6-point scale ranging from 0 (normal) to 5 (death associated with stroke). Brain histopathology was scored using a four-point scale on 19 of 30 rats surviving the 3-day postischemic neurologic examination and was correlated with neurologic deficit scores. Fasted rats had plasma glucose concentrations of 79 ± 7 mg/100 ml (mean ± SE) during ischemia and a significantly better neurologic outcome ($P < 0.001$) than glucose-loaded rats (plasma glucose = 496 ± 43 mg/100 ml). Nonfasted rats had blood glucose values (292 ± 28 mg/100 ml) and deficit scores not significantly different from fasted but better than glucose-loaded rats ($P = 0.054$). Brain histology showed the greatest neuronal damage in caudate followed by hippocampus and cortical tissue. Histopathologic evaluation showed a correlation of $r = 0.87$ ($P < 0.01$) with neurologic outcome. In separate experiments brain samples were collected at the end of the ischemic period in each of the experimental groups and regional tissue lactate and brain phosphocreatine and adenosinetriphosphate (ATP) concentrations were measured. Ischemic tissue lactate was similar in fasted, nonfasted, and glucose-loaded rats in caudate and hippocampus but was significantly higher in glucose loaded rats in cortical and thalamic tissue. Phosphocreatine and ATP were decreased by ischemia and were lower in fasted than in nonfasted and glucose-loaded rats. These results confirm previous reports that fasting and lower plasma glucose concentrations protect the brain from ischemic damage but question the influence of tissue lactate or maintenance of brain energy metabolites. (Key words: Anesthetics, volatile: isoflurane. Blood: glucose. Brain: ATP; EEG; glucose; ischemia; lactate; phosphocreatine.)

STUDIES evaluating complete or near-complete cerebral ischemia have shown that hyperglycemia worsens outcome.[1–7] However, there is controversy whether hyperglycemia is beneficial or detrimental during incomplete or focal brain ischemia or hypoxia.[8–13] It has been reported that brain lactate production during ischemia is a primary factor leading to stroke damage and neuronal death.[7,14,15] Hyperglycemia may produce greater brain tissue injury during ischemia by increasing brain lactate production and tissue acidosis.[16] However, this has not been tested adequately, particularly in models of incomplete cerebral ischemia. More recent studies have shown that although hypothermia markedly improves outcome and decreases neuronal death due to brain ischemia, this improvement is not associated with a reduction in brain lactate or free fatty acid production.[17,18] It was the purpose of the present study to evaluate the effect of fasting *versus* nonfasting *versus* glucose loading on neurologic and histopathologic outcome during incomplete ischemia in the rat and to correlate these end points with brain tissue lactate and brain energy state.

Methods

These experiments were approved by the Michael Reese Institutional Animal Care Committee. Overnight fasted and nonfasted male Sprague-Dawley rats were anesthetized with isoflurane in a bell jar. Following endotracheal intubation their lungs were ventilated with 1.7% inspired isoflurane in room air. Catheters were inserted into the femoral artery and veins and the right subclavian vein. Vecuronium was infused intravenously at a rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ to maintain paralysis. The right carotid artery was isolated for later clamping. The inspired isoflurane was then adjusted to 1.4%, which approximates 1 MAC in the rat, and maintained constant for 30 min.

Glucose loading was produced in nonfasted rats by injection of 50% glucose solution (6 ml/kg ip). Fasted and nonfasted rats received 8% sodium chloride (6 ml/kg ip) to control for the osmotic load (n = 10 per group). The animals were allowed 30 min for equilibration prior to induction of ischemia.

Cerebral ischemia was produced by clamping the right carotid artery and decreasing mean arterial blood pressure to 30 mmHg by hemorrhage. A range of 2 mmHg was allowed for the target pressure. Rectal temperature was maintained at 37° C and Pa_{CO_2} between 35 and 40 mmHg by adjusting ventilation. Arterial *p*H was maintained at normal levels by bicarbonate infusion. At the end of a 30-min ischemic period the carotid artery was unclamped

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Received from the Michael Reese Hospital and Medical Center, Chicago, Illinois, and the University of Illinois College of Medicine, Chicago, Illinois. Accepted for publication January 23, 1990.

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and the withdrawn blood slowly reinfused. Fasted rats also received a 1-ml intraperitoneal injection of 50% glucose at the end of ischemia to increase blood glucose concentrations back to control levels. Following a 30-min recovery period the catheters were removed, the incisions closed, and the trachea extubated. Arterial blood samples were taken at the end of the control, ischemic, and recovery periods for measurement of plasma glucose using a Yellow Springs glucose analyzer, and blood gas tensions were measured using an Instrumentation Laboratory System 1303 blood gas analyzer.

Neurologic Outcome

Neurologic deficits were scored every 8 h starting from 3 h postrecovery and continuing for 3 days. The evaluator was blinded to the treatment condition of ischemia. Deficits were scored as follows: 0 = normal; 1 = right paw adduction or abnormal posturing; 2 = lethargy combined with abnormal posturing; 3 = unilateral weakness or circling; 4 = stroke-related seizures; and 5 = stroke-related death. Stroke-related death was determined after a minimum of 3 h following extubation and was scored only if the rat showed progressive signs of stroke impairment.

Brain Histopathology

Those rats that survived the 3-day neurologic observation period were anesthetized with isoflurane for formalin perfusion. The chest was dissected opened and the rat killed by transcardial perfusion of 50 ml saline followed by 50 ml 10% buffered formalin using a 50 ml syringe. The brain was removed and stored in formalin for 1 week for later histologic examination. The forebrain was cut into coronal blocks, imbedded in paraffin, and 7-μm sections were cut and mounted on slides. These slides were stained using hematoxylin and eosin and examined in a blinded manner by a neuropathologist (C.T.) using light microscopy. Brain histopathology was evaluated in the ischemic hemisphere in coronal section at the level of the caudate nucleus. Neuronal damage was graded on a 5-point scale by the neuropathologist with the following markers: 0 = no observable neuronal death; 1 = scattered neuronal death; 2 = small focal damage in caudate and cortical areas; 3 = large infarcts involving 50% of ischemic hemisphere; and 4 = total hemisphere infarct.

Lactate, Glucose, and Energy Metabolites

Brain lactate, glucose, ATP, and phosphocreatine concentrations were measured after 29 min of ischemia in separate experiments. Each rat received one of the pretreatments described. A separate group of nonfasted rats was used in this study as nonischemic controls. These rats received the same surgery as the other groups, including carotid ligation, but they were maintained at normotensive blood pressures before brain fixation. Following the 30-min ischemic or control period in each group, brain tissue was fixed and enzymatic activity inactivated by applying an 0.8-s 10-kW focused microwave pulse to the head using a Toshiba experimental rat microwave. The brain was removed and frozen in liquid freon, and the following tissues were dissected from right and left hemispheres: frontal cortex, parietal cortex, caudate, hippocampus, and thalamus. Tissues were weighed and stored in a −80° C freezer. Blood samples were collected in liquid nitrogen during ischemia before brain fixation and treated in a manner similar to tissue samples. Blood and brain tissue samples were extracted in 0.3 M perchloric acid containing 1 mM EDTA followed by neutralization with 3 M KOH. Brain tissue and blood lactate, glucose, phosphocreatine, and ATP concentrations were measured according to previously reported techniques.[19] Separate brains were used to measure phosphocreatine and ATP *versus* lactate and glucose. Four rats per group were used for phosphocreatine and ATP measurements. For brain glucose and lactate, four rats per group were fasted or glucose-loaded and five rats per group were nonischemic controls or fed and ischemic.

Statistics

Parametric data are reported as mean ± SE. Nonparametric neurologic deficit scores were analyzed using a Kruskal-Wallis analysis of variance (ANOVA). Neurologic outcome was correlated with histopathologic scores using a Spearman rank-order correlation. Parametric data were analyzed using a two-way ANOVA and Scheffe's tests for multiple comparisons between groups.

Results

Blood pressure, heart rate, and blood gas tensions were similar among the three treatment groups under control conditions, during 15 and 30 min of ischemia, and after 15 min of recovery from ischemia (table 1). Pa_{CO_2} in nonfasted and glucose loaded rats was significantly higher at 15 and 30 min of ischemia compared with fasted rats. Blood glucose decreased to 79 ± 7 mg/100 ml during ischemia in fasted rats and increased to 292 ± 28 and 496 ± 43 mg/100 ml in nonfasted and glucose-loaded rats, respectively, after 30 min of ischemia (table 1). Neurologic outcome tests showed that glucose-loaded rats had a significantly worse deficit score following ischemia than fasted rats (fig. 1). Nonfasted rats were not significantly different from fasted rats but showed a difference from glucose-loaded rats at the $P = 0.054$ level. To correlate neurologic outcome with neuronal tissue damage, brain histopathology was evaluated in 19 of 30 rats that survived the 3-day neurologic outcome evaluation. These consisted

TABLE 1. Mean Arterial Blood Pressure, Heart Rate, Blood Gas Tensions, and Blood Glucose during Ischemia and Recovery

Treatment	Blood Pressure (mmHg)	Heart Rate (bpm)	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	pH	Plasma Glucose (mg/100 ml)
Fasted (n = 10)						
Control	70 ± 9	308 ± 10	36.8 ± 1.2	81 ± 4	7.40 ± 0.01	134 ± 7
15 min	31 ± 1*	357 ± 11	32.0 ± 1.1	96 ± 3	7.46 ± 0.02	102 ± 8
30 min	30 ± 1*	400 ± 15	33.9 ± 0.9	91 ± 3	7.45 ± 0.02	79 ± 7*
Recovery	88 ± 3	375 ± 13	38.7 ± 1.2	71 ± 3	7.39 ± 0.02	173 ± 15
Nonfasted (n = 10)						
Control	72 ± 7	317 ± 5	41.0 ± 1.2	78 ± 3	7.37 ± 0.01	176 ± 7
15 min	31 ± 1*	335 ± 18	38.4 ± 1.2†	95 ± 9	7.37 ± 0.02	304 ± 16*†
30 min	30 ± 1*	382 ± 8	39.2 ± 1.1†	83 ± 4	7.40 ± 0.02	292 ± 28*†
Recovery	81 ± 6	400 ± 12	40.0 ± 1.1	66 ± 4	7.42 ± 0.01	198 ± 22
Glucose (n = 10)						
Control	73 ± 6	330 ± 11	38.8 ± 1.1	88 ± 2	7.38 ± 0.02	474 ± 38†
15 min	31 ± 1*	315 ± 46	37.8 ± 1.8†	89 ± 2	7.38 ± 0.02	506 ± 38†
30 min	30 ± 1*	395 ± 14	39.4 ± 1.6†	89 ± 4	7.40 ± 0.02	496 ± 43†
Recovery	68 ± 4	405 ± 13	39.6 ± 1.1	68 ± 3	7.41 ± 0.02	398 ± 50†

Values are mean ± SE; 15 and 30 min represent the duration of cerebral ischemia.

* $P < 0.05$ *versus* control in each group.
† $P < 0.05$ *versus* fasted group.

of the nine fasted rats, seven nonfasted rats, and three glucose-loaded rats that survived the 3-day evaluation period. Neurologic deficits in these rats ranged from 0 to 4 and histopathologic scores ranged from 0 to 4. A Spearman rank-order correlation between these two parameters produced an r value of 0.87 ($P < 0.01$). Histology indicated that neuronal damage was located primarily in the caudate. In cases of severe stroke, the size of the infarction increased to include cortical tissue within the same coronal section, and occasionally the entire hemisphere was ablated. Even in these cases, the contralateral hemisphere showed little damage or perhaps scattered neuronal death, indicating minimal ischemic effects in this hemisphere. The hippocampus showed damage in the CA1 area, which was consistent with ischemic damage in the caudate, but thalamic tissue was less affected by ischemia.

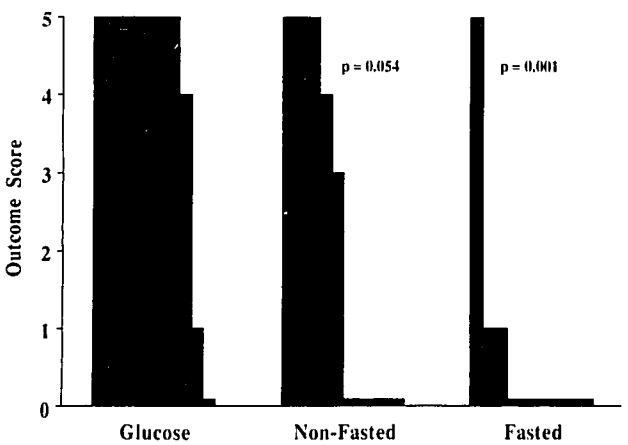

FIG. 1. Neurologic outcome in glucose-loaded, fed, and fasted rats. Each bar represents the highest score obtained in individual rats in each treatment group. Significance indicates the difference from glucose-loaded rats. The outcome scores of fed rats were not significantly different from fasted rats.

In separate experiments we measured brain tissue lactate, glucose, and energy metabolite concentrations during ischemia. Ischemia increased brain lactate in the cerebral hemisphere ipsilateral to carotid occlusion (table 2). Lactate concentrations were similar in the caudate and hippocampus of fasted, nonfasted, and glucose-loaded rats. In ischemic cortical and thalamic tissue, glucose-loaded rats showed 20–30% higher lactate concentrations than the other two groups. Blood lactate was elevated by hypotension and ischemia in all groups: nonischemic control = 0.61 ± 0.08 μmol/g, fasted ischemic = 2.70 ± 0.50 μmol/g, nonfasted ischemic = 3.72 ± 0.26 μmol/g, and glucose-loaded ischemic = 4.23 ± 0.3 μmol/g ($P < 0.01$ ischemic treatment groups *vs.* nonischemic controls, $P < 0.05$ fasted *vs.* glucose-loaded). Brain glucose was not depressed in ischemic nonfasted or glucose-loaded rats compared with nonischemic control rats, but fasted rats showed a significant decrease in brain glucose in both hemispheres during ischemia.

Phosphocreatine and ATP concentrations were significantly decreased in ischemic cortex, caudate, and hippocampus in all treatment groups compared with nonischemic controls (table 3). ATP decreased more in cortex and caudate than thalamus or hippocampus and fasted rats showed greater ATP depletion in these tissues compared with fed and glucose-loaded rats.

Discussion

In these studies enhanced glucose availability during ischemia in nonfasted and glucose-loaded rats preserved brain energy state better than in rats that were fasted. This suggests that hyperglycemia during ischemia protects

TABLE 2. Brain Lactate and Glucose Concentrations in Ischemic (right) and Nonischemic (left) Hemispheres

Group	Location	N	Cortex	Caudate	Thalamus	Hippocampus
Lactate (μmol/g)						
Control	Right	5	1.59 ± 0.13	2.38 ± 0.06	1.68 ± 0.16	1.74 ± 0.72
	Left		1.69 ± 0.19	2.16 ± 0.29	2.18 ± 0.15	3.31 ± 0.36
Fasted	Right	4	7.02 ± 0.14*	9.14 ± 0.65*	8.33 ± 0.20*	10.01 ± 0.69*
	Left		5.30 ± 1.27	5.50 ± 1.19	4.78 ± 1.37	7.45 ± 1.85*
Fed	Right	5	7.72 ± 0.92*	10.16 ± 1.57*	9.14 ± 0.65*	10.64 ± 1.05*
	Left		5.28 ± 1.10	5.21 ± 1.17	4.15 ± 0.79	6.83 ± 1.57
Glucose-loaded	Right	4	10.45 ± 0.72*†	10.64 ± 1.05*	13.30 ± 0.71*†	12.92 ± 0.69*
	Left		5.30 ± 0.96	4.86 ± 1.14	4.19 ± 0.91	6.01 ± 1.14
Glucose (μmol/g)						
Control	Right	5	2.74 ± 0.30	2.76 ± 0.33	2.81 ± 0.14	2.82 ± 0.06
	Left		2.79 ± 0.31	2.79 ± 0.15	2.81 ± 0.15	2.82 ± 0.06
Fasted	Right	4	0.27 ± 0.02*	0.09 ± 0.02*	0.19 ± 0.15*	0.14 ± 0.04*
	Left		0.50 ± 0.15*	0.53 ± 0.24*	0.57 ± 0.24*	0.58 ± 0.26*
Fed	Right	5	2.00 ± 0.67	1.17 ± 0.51	1.70 ± 0.55	1.15 ± 0.46
	Left		2.15 ± 0.57†	2.57 ± 0.67†	2.85 ± 0.52†	2.51 ± 0.80
Glucose-loaded	Right	4	2.02 ± 0.30	1.51 ± 0.31	2.35 ± 0.59†	2.09 ± 0.59†
	Left		3.52 ± 0.18†	4.43 ± 0.57†	5.37 ± 0.66†	5.51 ± 0.72†

Right = hemisphere ipsilateral to carotid occlusion; left = hemisphere contralateral to carotid occlusion.

* $P < 0.05$ *versus* nonischemic control.
† $P < 0.05$ *versus* fasted rats.

the brain from energy depletion. This agrees with *in vitro* studies indicating that hyperglycemia preserves neuronal function during hypoxia better than normoglycemia[9] and with *in vivo* studies showing that ATP decreases more in hypoglycemic rats compared with normoglycemic and hyperglycemic rats during ischemia.[13] However, the evaluation of neurologic outcome showed that hyperglycemia worsened long-term outcome from ischemia. This is consistent with studies indicating a worse outcome with hyperglycemic ischemia.[2–5] Together these results suggest that hyperglycemia protects the brain from energy state depletion during ischemia but produces more neuronal injury and a worse outcome in the long term.

The literature suggests that brain ischemia is associated with increased lactate formation and brain tissue acidosis, which are primarily responsible for neuronal injury.[20–22] However, our results question this suggestion. First, ischemic tissue lactate concentrations in different brain regions of each rat did not correlate well with ischemic injury. The caudate nucleus consistently showed the most ischemic damage in all groups tested, but lactate concentrations were not higher in the caudate compared with other regions. With respect to different treatment conditions, the lactate concentration in the caudate was not different between treatment groups but ischemic injury was consistently worse in this tissue in glucose-loaded and

TABLE 3. Brain Phosphocreatine and ATP Concentrations in Ischemic (right) and Nonischemic (left) Hemispheres

Group	Location	N	Cortex	Caudate	Thalamus	Hippocampus
Phosphocreatine (μmol/g)						
Control	Right	4	3.12 ± 0.25	3.43 ± 0.29	3.13 ± 0.35	3.15 ± 0.39
	Left		3.16 ± 0.29	3.23 ± 0.32	3.49 ± 0.29	3.39 ± 0.34
Fasted	Right	4	1.18 ± 0.24*	1.05 ± 0.33*	1.52 ± 0.53	1.23 ± 0.31*
	Left		4.12 ± 1.02	6.50 ± 1.39	3.30 ± 0.59	5.27 ± 1.40
Fed	Right	4	1.07 ± 0.26*	1.04 ± 0.41*	1.97 ± 0.48	1.02 ± 0.30*
	Left		4.56 ± 1.57	2.69 ± 0.37	3.83 ± 1.06	4.31 ± 1.70
Glucose-loaded	Right	4	1.57 ± 0.55	1.52 ± 0.51*	1.97 ± 0.48	1.02 ± 0.30*
	Left		4.06 ± 0.64	4.22 ± 0.18	3.42 ± 0.85	3.94 ± 0.48
ATP (μmol/g)						
Control	Right	4	3.07 ± 0.10	3.11 ± 0.16	3.00 ± 0.18	2.84 ± 0.15
	Left		3.04 ± 0.12	2.99 ± 0.22	3.13 ± 0.07	2.98 ± 0.37
Fasted	Right	4	0.46 ± 0.04*	0.53 ± 0.20*	2.21 ± 1.00	0.71 ± 0.07*
	Left		2.46 ± 0.43	3.39 ± 0.33	2.12 ± 0.45	2.33 ± 0.45
Fed	Right	4	1.30 ± 0.47*	1.40 ± 0.59	2.31 ± 0.53	1.12 ± 0.39*
	Left		3.12 ± 0.37	2.62 ± 0.30	2.50 ± 0.05	2.97 ± 0.48
Glucose-loaded	Right	4	0.99 ± 0.31*	1.40 ± 0.59	1.54 ± 0.39	1.49 ± 0.42
	Left		2.49 ± 0.47	2.34 ± 0.22	1.80 ± 0.24*	2.36 ± 0.20

* $P < 0.05$ *versus* nonischemic control.

fed rats compared with fasted rats. These results indicate that tissue lactate concentration is not an adequate marker of subsequent stroke injury in this ischemic model.

One of the major concerns of this study is the value that lactate may have as a marker of tissue acidosis in this model of incomplete cerebral ischemia. In models of complete or near-complete cerebral ischemia, lactate concentrations of 16–20 μmol/g or higher are reportedly necessary to cause direct neuronal injury.[20,23,24] Lactate is the primary marker of acid production during complete ischemia and other metabolic acids show little change during anaerobic glycolysis.[21,25] Because of this relationship, several investigators have indicated a direct correlation between tissue lactate concentration and tissue acidosis during ischemia.[21,22] However, lactate may not be a valid marker of tissue acidosis in this model of incomplete ischemia because lactate efflux may have occurred during ischemia. In this case lactate levels may underestimate the degree of tissue acidosis. Therefore, it is difficult to compare lactate levels in this study with levels seen during complete ischemia. It is expected that tissue lactate concentrations measured during complete ischemia may reflect tissue *p*H, but that may not be the case in our model.

One potential problem in this study is that tissue measurements of lactate, glucose, phosphocreatine, and ATP were not performed in the same rats in which outcome was evaluated. Thus, we were not able to determine whether variation in tissue lactate concentration within treatment groups was an important factor in determining outcome. This would be a major problem if our data were widely variable. However, regional lactate concentrations were consistent within treatment groups. The only treatment group in which lactate concentration differences may have been predictive of outcome was the nonfasted rats, which showed an equal number of severe and nonsevere stroke deficits. However, this does not explain how fasted rats had a better outcome but showed similar brain lactate concentrations as nonfasted rats.

Hypertonic saline was used in these studies to control for the osmotic effect of glucose administration in the hyperglycemic group. Although osmotically the hypertonic saline and glucose treatments are equal, the effect on the brain may be dissimilar. Intraperitoneal hypertonic saline will produce hypervolemia as water is drawn from the blood into the intraperitoneal space and subsequent prolonged hypernatremia and brain dehydration take place. Initially, a similar brain dehydration will be seen with hyperglycemia. However, the glucose concentration will equilibrate across the blood–brain barrier, attenuating the blood to brain osmotic difference sooner. In short, the time course of the osmotic load produced by hypertonic saline and hypertonic glucose will not be the same. However, the use of hypertonic saline to control for osmotic changes is more appropriate than no treatment at all. The administration of a small glucose load in fasted rats after the ischemic event may have been unnecessary. Glucose was given to return blood concentrations to control levels after ischemia. However, it is possible that glucose delivery affected postischemic recovery and worsened neurologic outcome in the fasted rats.

One finding that is difficult to explain in this study is that glucose-loaded rats had higher cortical and thalamic lactate concentrations than fed rats even though tissue glucose availability was not limited in either group. If glucose availability is adequate in both groups, higher tissue lactate concentrations in glucose-loaded rats should indicate a greater degree of ischemia. Other investigators have reported a direct cerebral vasoconstrictor effect of hyperglycemia.[26–28] If a glucose-related vasoconstriction were present in this study, it would explain the difference in tissue lactate concentration between treatment groups.

Histopathology was evaluated in rats that survived the 3-day neurologic examination. An inadequate number of rats survived from the glucose and fed treatment groups to allow statistical comparison of histologic scoring. A Spearman rank-order correlation demonstrated a significant correlation between neurologic outcome and histopathologic scores in all rats that survived. This supports the use of neurologic outcome scores as a measure of stroke damage. However, an inability to show significant differences in outcome between fed and fasted rats may indicate that the sensitivity of the neurologic scale was not adequate.

In conclusion, our results show that hyperglycemia will worsen outcome in a model in which ischemic blood flow is 30–40 ml/100 g.[29] This supports previous reports showing that hyperglycemia will increase brain injury associated with complete or near-complete ischemia.[6,7] Our results differ from work using more complete ischemia in that our ischemic brain tissue lactate concentrations were similar between hyperglycemic and fasted rats. It is unlikely that blood lactate contributed to the elevated tissue lactate concentrations during ischemia because the concentration gradient was in the opposite direction. However, it is possible that lactate moved from the brain to the blood during ischemia. This may explain the lack of difference in tissue lactate concentration between treatment groups, and it suggests that tissue lactate may underestimate tissue acidosis. Direct measurement of brain tissue *p*H may be necessary to resolve this issue.

The authors wish to thank Susan Anderson for her technical assistance in this work.

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