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The Effects of Insulin Infusion on Plasma and Brain Glucose in Hyperglycemic Diabetic Rats

A Comparison with Placebo-treated Diabetic and Nondiabetic Rats

Roger E. Hofer, M.D., William L. Lanier, M.D.†*

Experimental and clinical studies have revealed a worsened neurologic outcome after cerebral ischemia in hyperglycemic subjects, including hyperglycemic diabetic subjects. A possible therapy to reduce the magnitude of ischemic brain injury in diabetic subjects would be to use an insulin infusion to reduce brain glucose concentrations to values found in those who are normoglycemic and nondiabetic. The present study, using hyperglycemic diabetic rats, examined the effect of an insulin infusion on plasma and brain glucose concentrations to determine their relationship while plasma glucose concentrations decreased. In addition, plasma and brain glucose concentrations were compared to those in diabetic and nondiabetic rats treated with saline. Saline had no effect on the plasma or brain glucose concentrations in the diabetic rats or nondiabetic rats. The saline-treated diabetic rats had increased plasma and brain glucose concentrations as well as an increased brain-to-plasma glucose ratio when compared to the saline-treated nondiabetic rats. When an insulin infusion was used in diabetic rats to decrease plasma glucose to nondiabetic levels over approximately 2 h, the brain glucose concentration decreased. However, the brain-to-plasma glucose ratio remained at the "diabetic" value, so that the brain glucose concentration tended to remain increased when compared to normoglycemic, nondiabetic rats. We conclude that if these results are applicable to humans, measurement of plasma glucose in diabetic patients will underestimate the amount of glucose in the brain and this relationship will not be influenced by acute insulin therapy. (Key words: Brain: glucose; ischemia. Metabolism: diabetes; hyperglycemia; insulin; streptozocin. Plasma: glucose.)

HYPERGLYCEMIA and increases in brain glucose will exacerbate cerebral injury after a period of ischemia.[1–6] An increase in brain glucose also may contribute to the worsened neurologic outcome in untreated diabetic patients after resuscitation from cardiac arrest[3,4]; however, there is some controversy regarding the mechanism by which this exacerbated injury occurs.[7] The effect of insulin treatment on increased plasma and brain glucose concentrations in diabetic subjects and the effect of insulin therapy (to produce normoglycemia) on postischemic neurologic injury in diabetics, have not been previously investigated.

* Instructor in Anesthesiology.

† Associate Professor of Anesthesiology.

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Address reprint requests to Dr. Lanier: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55905.

Previously reported data have suggested that insulin therapy may result in an increase in the brain-to-blood glucose ratio (Gl_{br}/Gl_{bl}) as blood glucose (Gl_{bl}) declines.[8] If this is true, cerebral ischemia after the attainment of normoglycemia by insulin treatment of diabetic hyperglycemia could be associated with a worsened neurologic outcome, as compared to that of normoglycemic nondiabetic subjects. We examined the effect of insulin treatment on plasma (Gl_{pl}) and brain glucose (Gl_{br}) in hyperglycemic diabetic rats to determine whether acute restoration of Gl_{pl} to normoglycemic values would result in a restoration of normal Gl_{br} values.

Materials and Methods

This protocol was reviewed and approved by the Institutional Animal Care and Use Committee. Subjects were 66 Sprague-Dawley rats weighing 275–325 g. One week before the study, diabetes was induced in 42 rats with intraperitoneal streptozocin 60 $mg \cdot kg^{-1}$.[9] All rats were fasted for 10–12 h before the study but had free access to water. The rats were weighed and then anesthetized in an induction box with 3% halothane in oxygen. After induction of anesthesia and tracheostomy, the trachea was intubated, and the lungs were mechanically ventilated with a rodent ventilator (Ugo Basile, Model 7025, Varese, Italy). Pancuronium 0.5 mg intramuscularly was given to provide muscle paralysis, and thereafter, anesthesia was maintained with 1.3% inspired halothane (a surgical anesthetic dose[10]) in nitrogen and oxygen for the remainder of the study. The inspired oxygen and halothane concentrations were measured with a RASCAL® laser-type gas analyzer (Albion Instruments, Salt Lake City, UT).

Temperature was measured using a rectal thermistor (model 73A, Yellow Springs Instruments, Yellow Springs, OH) and maintained at 37° C with a heating lamp and pad. The femoral artery was cannulated with a polyethylene catheter (PE-50) for blood sampling and measurement of mean arterial pressure. The femoral vein was cannulated (with a PE-50 cannula) for the administration of fluids and drugs. Arterial blood gases were determined using electrodes at 37° C (Instrumentation Laboratories, Lexington, MA). Gl_{bl} and Gl_{pl} were measured using a Yellow Springs model 23A glucose analyzer. This device has

a detection range of 0–28 $\mu mol \cdot ml^{-1}$ (0–500 $mg \cdot dl^{-1}$) and a sensitivity of 0.1 $\mu mol \cdot ml^{-1}$ (1 $mg \cdot dl^{-1}$).‡

The rat was placed prone and its head placed in a stereotactic headframe. The skin of the scalp was reflected, exposing the calvarium, and a funnel was secured to the exposed bone.[11] The bottom of the funnel was filled with a sheet of paraffin to prevent heat and moisture loss. Thereafter, 10-min periods were allowed, after each of which the anesthetic agent, ventilation, and oxygenation were adjusted until the changes resulted in data within predetermined protocol criteria: arterial carbon dioxide tension 38 ± 2 mmHg, arterial oxygen tension 150 ± 25 mmHg, mean arterial pressure >60 mmHg, temperature 37 ± 0.5° C, and inspired halothane concentration 1.3 ± 0.1%. Inclusion into the diabetic or nondiabetic groups was based upon the following criteria: diabetic rats were required to have a $Gl_{bl} > 200$ $mg \cdot dl^{-1}$ and nondiabetic rats were required to have a Gl_{bl} of > 60 but < 120 $mg \cdot dl^{-1}$ before any intervention. All study animals were allowed at least 20 min for stabilization after the completion of the surgical preparation.

According to the presence of diabetes-induced hyperglycemia, fluid infusion, and the time interval until brain harvesting for analysis, rats were divided into five groups: 1) nondiabetic control rats that received no fluid infusion (n = 6); 2) diabetic control rats that received no fluid infusion (n = 6); 3) nondiabetic rats treated with saline (n = 18); 4) diabetic rats treated with saline (n = 18); and 5) diabetic rats treated with insulin (n = 18).

The first two groups contained six nondiabetic and six diabetic rats, respectively. They received no fluid infusion. After at least 20 min of stabilization, and once the physiologic variables were within the protocol ranges, physiologic variables were recorded. The arterial blood was then sampled for measurement of blood gases, acid–base status, and Gl_{bl} and Gl_{pl}. Concomitantly, the brains were rapidly frozen *in situ* by removing the insulation covering the exposed calvarium and filling the funnel with liquid nitrogen.[11] The time of blood sampling and brain freezing in control rats was defined as time = 0 min. Liquid nitrogen was used to bathe the brains during removal as well as during transportation to temporary storage in a −76° C freezer. Later the brains were removed to a −25° C environment; the venous sinuses and meninges were dissected away; the hemispheres were separated from each other; and the cortex was dissected from the remainder of the cerebrum. Gl_{br} concentrations in the cortex were measured using a previously described enzymatic fluorometric technique.[12,13] This technique has a sensitivity of 0.2 $\mu mol \cdot g^{-1}$ [14] and a coefficient of variation of 3% (previously unpublished laboratory data).

‡ Model 23A Glucose Analyzer Instrument Manual. Yellow Springs Instrument Company, Inc., Yellow Springs, Ohio.

The next two groups of rats consisted of 18 saline-treated nondiabetic rats and 18 saline-treated diabetic rats. Each rat received an infusion of 0.9% sodium chloride solution at 2 $ml \cdot h^{-1}$ after the stabilization period. Six nondiabetic and 6 diabetic rats received an infusion of saline for 60 min. At the end of this time period, physiologic variables were recorded and the blood and brain were sampled as described in the control groups. Another 6 nondiabetic and 6 diabetic rats received the saline infusion for 90 min, and another 6 nondiabetic and 6 diabetic rats received saline for 120 min before blood and brain sampling.

The final 18 diabetic rats also received a saline infusion at a rate of 2 $ml \cdot h^{-1}$. However, regular porcine/bovine insulin (Eli Lilly & Co., Indianapolis, IN) was added to the saline solution to provide a delivery of insulin at 0.75 $U \cdot h^{-1}$. In pilot studies it was determined that, at this concentration and rate, insulin infusion for approximately 2 h would result in normoglycemia (*i.e.*, a Gl_{bl} between 60 and 120 $mg \cdot dl^{-1}$). Six diabetic rats received the insulin infusion for 60 min, another 6 diabetic rats for 90 min, and the remaining 6 diabetic rats for 120 min before blood and brain sampling.

Data between and within groups were compared using a two-way analysis of variance and unpaired *t* tests. The Pearson product-moment correlation coefficient was used to determine the relationship between Gl_{bl} and Gl_{pl} and between Gl_{pl} and Gl_{br}. In all comparisons, $P < 0.05$ was considered significant. All data are presented as mean ± standard deviation.

Results

Groups were well matched for systemic physiologic variables throughout the study with few exceptions. Diabetic rats lost 25–80 g weight in the week after streptozocin injection despite ample access to rat chow and water. The study weight in nondiabetic rats was 293 ± 17 g and in diabetic rats was 267 ± 19 g ($P < 0.01$ by unpaired *t* tests). The diabetic rats treated with saline for 60 min had a significantly lower *p*H than did their nondiabetic counterparts (table 1). The mean arterial pressures of the saline-treated diabetic rats at 60, 90, and 120 min and the insulin-treated diabetic rats at 60 min were significantly less than the nondiabetic rat groups at the same time period (table 1).

Both Gl_{bl} and Gl_{pl} were measured in all rats. In the first analysis, we examined the relationship between Gl_{bl} and Gl_{pl}. The correlation coefficient for the relationship between Gl_{bl} and Gl_{pl} in all diabetic and nondiabetic rats regardless of treatment was 0.99 ($P < 0.0001$ by *t* test). The relationship can be described by the equation: $Gl_{bl} = 11 \times Gl_{pl} + 1.9$, where Gl_{bl} and Gl_{pl} are expressed as micromoles per milliliter. Because of this close relation-

TABLE 1. Physiologic Variables at the Time of Plamsa and Brain Sampling in Halothane-anesthetized Diabetic and Nondiabetic Rats

Time of Sampling (min)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pH	MAP (mmHg)	Plasma Glucose ($\mu mol \cdot ml^{-1}$)	Brain Glucose ($\mu mol \cdot g^{-1}$)	Gl_{br}/Gl_{pl}
Nondiabetic rats							
Control	160 ± 24	40 ± 5	7.36 ± 0.04	84 ± 13	8.21 ± 0.97	2.07 ± 0.29	0.25 ± 0.03
Saline-treated							
60	149 ± 16	38 ± 3	7.33 ± 0.03	80 ± 5	6.84 ± 1.02	1.60 ± 0.44	0.23 ± 0.04
90	145 ± 11	39 ± 3	7.36 ± 0.03	78 ± 10	8.08 ± 1.87	1.75 ± 0.50	0.22 ± 0.04
120	138 ± 9	38 ± 5	7.36 ± 0.03	82 ± 9	8.02 ± 1.09	2.01 ± 0.24	0.25 ± 0.01
Diabetic rats							
Control	144 ± 9	40 ± 3	7.30 ± 0.08	67 ± 7†	24.99 ± 1.61†	8.11 ± 1.09†	0.32 ± 0.04†
Saline-treated							
60	146 ± 12	43 ± 10	7.27 ± 0.12†	61 ± 9†	27.82 ± 4.51†	9.46 ± 2.19†	0.35 ± 0.09†
90	150 ± 18	39 ± 4	7.36 ± 0.02	64 ± 6†	24.05 ± 2.03†	7.20 ± 0.79†	0.30 ± 0.03†
120	137 ± 13	40 ± 4	7.30 ± 0.05	67 ± 5†	24.73 ± 3.66†	8.07 ± 0.32†	0.32 ± 0.04†
Insulin-treated							
60	142 ± 7	39 ± 4	7.34 ± 0.05	64 ± 6†	18.39 ± 5.90*†	6.24 ± 2.04*†	0.34 ± 0.04†
90	142 ± 11	40 ± 3	7.37 ± 0.05	72 ± 10	12.36 ± 4.83*†	3.93 ± 1.81*†	0.31 ± 0.07†
120	141 ± 12	41 ± 3	7.38 ± 0.06	72 ± 8	10.15 ± 3.41*	3.34 ± 1.42*	0.32 ± 0.04†

All data are presented as mean ± SD.
Pa_{O_2}, Pa_{CO_2}, pH, and plasma glucose are from arterial samples.
MAP = mean arterial pressure; Gl_{br}/Gl_{pl} = brain-to-plasma glucose ratio.
* $P < 0.05$ *versus* respective control rats.
† $P < 0.05$ *versus* nondiabetic rats at the comparable time period.

ship, we elected to report primarily Gl_{pl} data. The relationship of Gl_{pl} to Gl_{br}, again in all rats, was also examined. There was a close relationship between plasma and Gl_{br} concentrations ($r = 0.95$; $P < 0.0001$ by t test). This relationship can be described by the formula: $Gl_{br} = 0.35 \times Gl_{pl} - 0.65$, where Gl_{br} is expressed as micromoles per gram and Gl_{pl} is expressed as micromoles per milliliter.

In the nondiabetic rats that did not receive a fluid infusion, Gl_{pl} at the time of brain harvesting was 8.21 ± 0.97 $\mu mol \cdot ml^{-1}$ and Gl_{br} was 2.07 ± 0.29 $\mu mol \cdot g^{-1}$ (table 1 and figs. 1 and 2). In saline-treated nondiabetic rats, the infusion had no significant effect on Gl_{pl}, Gl_{br}, or the brain-to-plasma glucose ratio (Gl_{br}/Gl_{pl}) (table 1 and figs. 1–3).

As expected, the untreated diabetic control rats had a significantly greater Gl_{pl} (24.99 ± 1.61 $\mu mol \cdot ml^{-1}$) and Gl_{br} (8.11 ± 1.09 $\mu mol \cdot g^{-1}$) than did the untreated nondiabetic rats ($P < 0.0001$ and $P < 0.001$, respectively) (table 1). Furthermore, Gl_{br}/Gl_{pl} was significantly greater in diabetic control rats (0.32 ± 0.04) than in nondiabetic

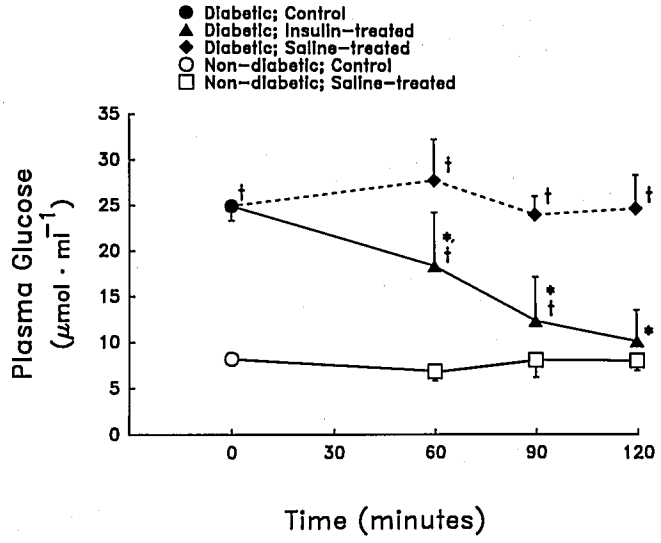

FIG. 1. Plasma glucose after saline infusion in diabetic and nondiabetic rats and after insulin infusion in diabetic rats. n = 6 for all data points. All values are presented as mean ± SD. *$P < 0.05$ from the control values; †$P < 0.05$ from nondiabetic rats at the same time period.

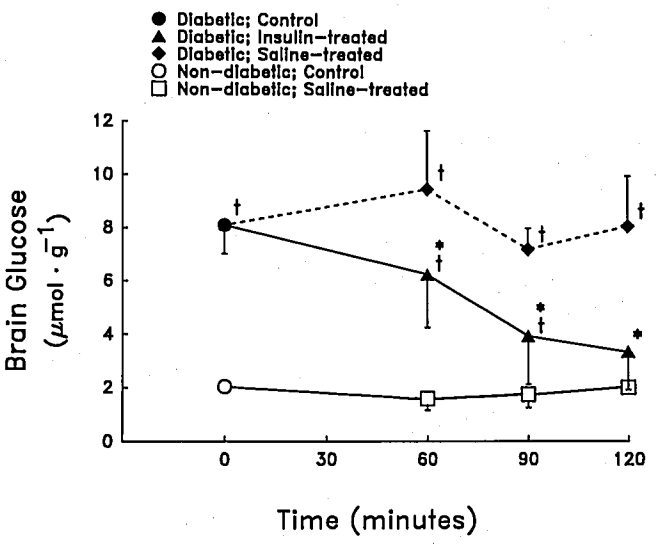

FIG. 2. Brain glucose after saline infusion in diabetic and nondiabetic rats and after insulin infusion in diabetic rats. n = 6 for all data points. All values are presented as mean ± SD. *$P < 0.05$ from the control values; †$P < 0.05$ from nondiabetic rats at the same time period.

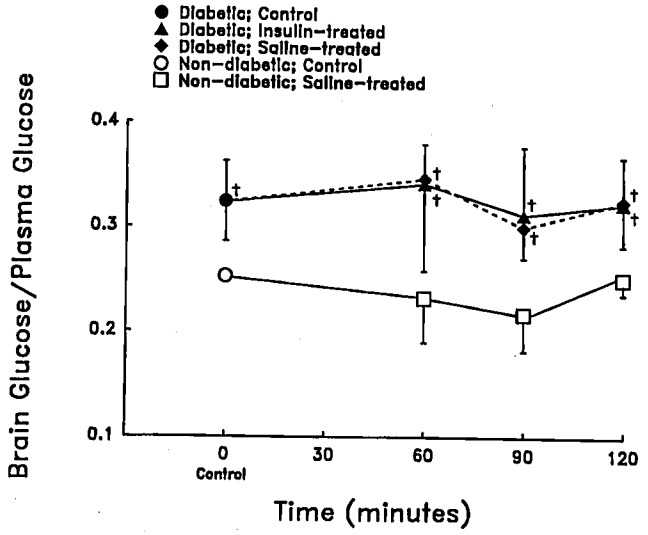

FIG. 3. Brain-to-plasma glucose ratio after saline infusion in diabetic and nondiabetic rats and after insulin infusion in diabetic rats. n = 6 for all data points. All values are presented as mean ± SD. †$P < 0.05$ from nondiabetic rats at the same time period. Neither saline nor insulin infusion affected the brain-to-plasma glucose ratio.

control rats (0.25 ± 0.03; $P < 0.001$)(table 1). Saline treatment in the saline-treated diabetic group had no effect on Gl_{pl}, Gl_{br}, or Gl_{br}/Gl_{pl} compared to those of the untreated diabetic group; however, all values were significantly greater when compared to saline-treated nondiabetic rats at the same time intervals (table 1 and figs. 1–3).

In the insulin-treated diabetic rats, the Gl_{pl} decreased to normoglycemic levels (10.15 ± 3.41 $\mu mol \cdot ml^{-1}$) by 120 min (table 1 and fig. 1). The Gl_{br} at 120 min in these rats (3.34 ± 1.42 $\mu mol \cdot g^{-1}$) was significantly less than that of the diabetic control rats ($P < 0.0001$). Despite this insulin-induced reduction in Gl_{br}, there was a strong tendency for the Gl_{br} concentration in the insulin-treated diabetic group at 120 min to differ from that of the nondiabetic saline-treated group at the same time period ($P = 0.058$) (table 1 and fig. 2). The Gl_{br}/Gl_{pl} in all diabetic rats, regardless of the type of infusion, was always significantly greater than in the nondiabetic rats (table 1 and fig. 3); however, there was no significant difference in Gl_{br}/Gl_{pl} between saline-treated and insulin-treated diabetic groups (table 1 and fig. 3).

Discussion

Clinical and experimental data have demonstrated that when the brain of humans[3,4] or laboratory animals[1,5,6] is exposed to ischemia during periods of hyperglycemia, the resulting neurologic injury is greater than that in normoglycemic subjects experiencing a comparable duration of ischemia.[2] During periods of hyperglycemia, glucose rapidly crosses the blood–brain barrier by facilitated diffusion and other secondary mechanisms,[15] producing elevated Gl_{br}.[1,6,14,16–18] If the brain is exposed to ischemia, it will anaerobically metabolize the available glucose to lactic acid.[5,18] Experimental evidence suggests that it is the resulting increase in lactic acid production that appears to be the metabolic toxin responsible for hyperglycemic augmentation of ischemic neurologic injury,[18,19] although this issue is controversial.[20,21]

Clinically, if monitoring of glucose is desired, we cannot measure Gl_{br}, but rather we measure Gl_{bl} or Gl_{pl} and assume there is a correlation between these variables and Gl_{br}. Studies have shown that as Gl_{bl} or Gl_{pl} increases, the Gl_{br} also increases.[1,14,18] Similarly, when Gl_{bl} or Gl_{pl} decreases under the influence of insulin, the Gl_{br} also tends to decrease.[22] Our data support these conclusions but additionally demonstrate that for a given Gl_{pl}, insulin-treated diabetic rats had a greater amount of glucose in the brain than did normoglycemic nondiabetic rats.

In our study, the accumulation of glucose in the brain of insulin-treated diabetic rats appeared to be due not to a lack of equilibrium between Gl_{bl} and Gl_{br} concentrations induced by rapid glucose changes or to the influence of insulin therapy, but instead to the diabetic state itself. These conclusions are supported by several recent studies. Pelligrino *et al.*, in a study in rats having streptozocin-induced diabetes of 6–8-week duration, also noted an accumulation of glucose in the brains of insulin-treated diabetic rats when normoglycemia was obtained after 0.5 h of insulin treatment.[23] In addition, in three pilot rats, glucose accumulation in the brain was observed if insulin therapy, and thus normoglycemia, continued for 18–24 h.[23] This suggests that a failure to attain equilibrium between Gl_{bl} and Gl_{br} during rapid glucose fluxes was not the cause of the glucose accumulation in our study or that of Pelligrino *et al.*

A failure of Gl_{bl} and Gl_{br} concentrations to reach equilibrium can occur in the rat during periods of rapidly decreasing Gl_{bl}, as recently demonstrated by Weglinski and Lanier.[14] However, this inability to achieve equilibrium (*i.e.*, hysteresis) occurs during glucose fluxes of much greater magnitude than that observed during insulin therapy in the present study.[14] When this lack of equilibrium occurs, it is manifested as an alteration in Gl_{br}/Gl_{pl}.[14] In the present study, the Gl_{br}/Gl_{pl} did not change with insulin infusion in diabetic rats, and Gl_{br}/Gl_{pl} did not differ between insulin- and saline-treated diabetic rats. The latter observation suggests that insulin infusion *per se* was not responsible for Gl_{br} accumulation in diabetic rats. Finally, follow-up studies in our laboratory have evaluated the relationship between Gl_{br} and Gl_{pl} in biologically bred diabetic rats and compared those results to saline-treated biologically bred nondiabetic litter mates.[24] The results

of these studies confirm our results in streptozocin-treated diabetic rats and additionally rule out streptozocin treatment as the cause of Gl_{br} accumulation.

Although the mechanism by which the diabetic brain accumulates more glucose than the nondiabetic brain is not clear, this finding may have important clinical implications. The occurrence of chronic and subacute hyperglycemia in the perioperative period is common and is due to a variety of conditions, including diabetes, stress, and the use of corticosteroids.[17] Furthermore, surgical patients may experience brain ischemia, either inadvertently (*e.g.*, accompanying cardiac arrest) or as a planned clinical management that may include circulatory arrest for the surgical treatment of complex cardiovascular and neurovascular abnormalities. It is known that hyperglycemia exacerbates ischemic neurologic injury. Based on the previously proposed mechanism and previous data from a primate model of global ischemia,[1] for a given degree of brain ischemia there is a correlation between Gl_{br} and the severity of the postischemic neurologic injury. By reducing Gl_{br} concentrations in hyperglycemic patients to values found in normoglycemic patients, it may be possible to reduce ischemic brain injury. However, if one monitors Gl_{bl} or Gl_{pl} during restoration of normoglycemia, and those values underestimate the Gl_{br} reduction, this in turn may lead to an underestimation of the potential for ischemic neurologic injury. This phenomenon has been demonstrated in previous studies from our laboratory examining Gl_{br} and ischemic neurologic injury in subjects studied after transient glucose infusions. In the latter setting, Gl_{bl} declined faster than Gl_{br}, and thus, underestimated Gl_{br}.[1,14]

In the present study, some of the saline-treated diabetic rats had significantly lower arterial blood *p*H values than did nondiabetic rats treated with saline for the same duration (table 1). This *p*H reduction was due probably to slight ketoacidosis in untreated diabetic rats. Although acute intracellular acidosis resulting from the anaerobic metabolism of glucose (presumably originating in the mitochondria) has been suggested as a determining or contributing factor in the cellular damage associated with cerebral ischemia,[21] the effect of a preexisting systemic acidosis on neurologic outcome after cerebral ischemia is unknown.

It has previously been reported that hyperglycemic diabetic subjects have a worsened outcome after global brain ischemia (*i.e.*, cardiac arrest) than do normoglycemic nondiabetic subjects.[3,4] Based on existing data, it is unlikely that the rapid reduction in Gl_{bl} before brain ischemia will reduce the diabetic patient's risk of brain injury to values consistent with a normoglycemic, nondiabetic patient, for several reasons. First, diabetes produces chronic cerebrovascular and hemorheologic changes that in turn may impair the ability of the brain to recover from an ischemic event.§ Second, the rapid reduction of G_{bl} in chronically diabetic subjects may result in a state of cerebral hypermetabolism,[23] a condition that in itself may have an adverse effect on the ischemic brain. Third, our data suggest that the acute restoration of normal G_{bl} or G_p in chronically diabetic subjects may not result in a complete restoration of a normal G_{br}. Taken together, these studies suggest that acute restoration of normoglycemia in chronically diabetic subjects may be insufficient to return the risk of ischemic brain injury to a level found in nondiabetic subjects. We hypothesize that the use of insulin to treat diabetes may result in some improvement in global ischemic injury when compared to untreated diabetic subjects; however, the magnitude of this improvement must be further evaluated.

The present study demonstrated that when insulin was used to achieve normoglycemia in rats previously made diabetic, they had a greater amount of glucose in the brain than did normoglycemic, nondiabetic subjects. Our data suggest that this increased G_{br} is produced by an alteration in the manner in which the diabetic brain handles glucose (the diabetic brain appears to store glucose) and not by an insulin effect or a lack of equilibrium between G_{bl} and G_{br} concentrations. The mechanism of the alteration in which the diabetic brain handles glucose is still unclear. It was once believed that the diabetic state caused a slowing of the blood–brain barrier transport of glucose.[5,25,26] Recently, it has been reported that there is actually an increase in activity of the blood–brain barrier glucose transporter[23,27,28] and that this phenomenon may be linked to a change in mRNA activity.[28] Nonetheless, regardless of the mechanism, the present study reveals that insulin-treated diabetic subjects have an increased Gl_{br}/Gl_p and an apparent glucose accumulation in the brain when compared to nondiabetic subjects. Therefore, if we assume that the degree of neurologic injury that follows a period of complete cerebral ischemia is proportional to the degree of increased G_{br}, we conclude that the measurement of G_{bl} or G_p in acutely insulin-treated, normoglycemic diabetics will underestimate both the G_{br} and the degree of postischemic neurologic injury.

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