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

A Comparison with Placebo-treated Diabetic and Nondiabetic Rats

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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.8,4; 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.

Previously reported data have suggested that insulin therapy may result in an increase in the brain-to-blood glucose ratio (Glb/Gbl) as blood glucose (Gbl) 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 (Gpl) and brain glucose (Glb) in hyperglycemic diabetic rats to determine whether acute restoration of Gpl to normoglycemic values would result in a restoration of normal Glb 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 275–925 g. One week before the study, diabetes was induced in 42 rats with intraperitoneal streptozocin 60 mg·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 1.9% inspired halothane (a surgical anesthetic dose10) 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). Gpl and Gbl were measured using a Yellow Springs model 28A glucose analyzer. This device has
a detection range of 0–28 μmol·ml⁻¹ (0–500 mg·dl⁻¹) and a sensitivity of 0.1 μmol·ml⁻¹ (1 mg·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. 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 Glbd > 200 mg·dl⁻¹ and nondiabetic rats were required to have a Glbd of > 60 but < 120 mg·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 Gld and Glpt. Concomitantly, the brains were rapidly frozen in situ by removing the insulation covering the exposed calvarium and filling the funnel with liquid nitrogen. 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. Gtamb concentrations in the cortex were measured using a previously described enzymatic fluorometric technique. This technique has a sensitivity of 0.2 μmol·g⁻¹ and a coefficient of variation of 3% (previously unpublished laboratory data).

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·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·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·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 Glbd between 60 and 120 mg·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 Gld and Gtd and between Gtamb and Gtamb. 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 pH 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 Glbd and Glpt were measured in all rats. In the first analysis, we examined the relationship between Gtd and Gtamb. The correlation coefficient for the relationship between Gtd and Gtamb 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: Gtd = 11 × Gtamb + 1.9, where Gtd and Gtamb are expressed as micromoles per milliliter. Because of this close relation-

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

<table>
<thead>
<tr>
<th>Time of Sampling (min)</th>
<th>$P_{gO_2}$ (mmHg)</th>
<th>$P_{gCO_2}$ (mmHg)</th>
<th>pH</th>
<th>MAP (mmHg)</th>
<th>Plasma Glucose (µmol·mL$^{-1}$)</th>
<th>Brain Glucose (µmol·g$^{-1}$)</th>
<th>Glbr/Gpl ratio</th>
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<tbody>
<tr>
<td><strong>Nondiabetic rats</strong></td>
<td></td>
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<tr>
<td>Control</td>
<td>160 ± 24</td>
<td>40 ± 5</td>
<td>7.36 ± 0.04</td>
<td>84 ± 13</td>
<td>8.21 ± 0.97</td>
<td>2.07 ± 0.29</td>
<td>0.25 ± 0.08</td>
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<tr>
<td>Saline-treated</td>
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<tr>
<td>60</td>
<td>149 ± 16</td>
<td>38 ± 3</td>
<td>7.33 ± 0.03</td>
<td>80 ± 5</td>
<td>6.84 ± 1.02</td>
<td>1.60 ± 0.44</td>
<td>0.23 ± 0.04</td>
</tr>
<tr>
<td>90</td>
<td>145 ± 11</td>
<td>39 ± 3</td>
<td>7.36 ± 0.03</td>
<td>78 ± 10</td>
<td>6.74 ± 1.08</td>
<td>1.75 ± 0.50</td>
<td>0.22 ± 0.04</td>
</tr>
<tr>
<td>120</td>
<td>138 ± 9</td>
<td>36 ± 5</td>
<td>7.36 ± 0.03</td>
<td>82 ± 9</td>
<td>6.02 ± 1.09</td>
<td>2.01 ± 0.24</td>
<td>0.25 ± 0.01</td>
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<tr>
<td><strong>Diabetic rats</strong></td>
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<tr>
<td>Control</td>
<td>144 ± 9</td>
<td>40 ± 3</td>
<td>7.30 ± 0.08</td>
<td>67 ± 7†</td>
<td>24.99 ± 1.61†</td>
<td>8.11 ± 1.09†</td>
<td>0.32 ± 0.04†</td>
</tr>
<tr>
<td>Saline-treated</td>
<td></td>
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<tr>
<td>60</td>
<td>146 ± 12</td>
<td>43 ± 10</td>
<td>7.27 ± 0.12†</td>
<td>61 ± 9†</td>
<td>27.62 ± 4.51†</td>
<td>9.46 ± 2.19†</td>
<td>0.55 ± 0.09†</td>
</tr>
<tr>
<td>90</td>
<td>150 ± 18</td>
<td>39 ± 4</td>
<td>7.36 ± 0.02</td>
<td>64 ± 6†</td>
<td>24.05 ± 2.03†</td>
<td>7.20 ± 0.79†</td>
<td>0.30 ± 0.03†</td>
</tr>
<tr>
<td>120</td>
<td>137 ± 13</td>
<td>40 ± 4</td>
<td>7.30 ± 0.05</td>
<td>67 ± 5†</td>
<td>24.73 ± 3.65†</td>
<td>8.07 ± 0.52†</td>
<td>0.32 ± 0.04†</td>
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<tr>
<td><strong>Insulin-treated</strong></td>
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</tr>
<tr>
<td>60</td>
<td>142 ± 7</td>
<td>39 ± 4</td>
<td>7.34 ± 0.05</td>
<td>64 ± 6†</td>
<td>18.39 ± 5.90†</td>
<td>6.24 ± 2.04†</td>
<td>0.34 ± 0.04†</td>
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<tr>
<td>90</td>
<td>142 ± 11</td>
<td>40 ± 3</td>
<td>7.37 ± 0.05</td>
<td>72 ± 10</td>
<td>12.56 ± 4.83†</td>
<td>5.39 ± 1.81†</td>
<td>0.31 ± 0.07†</td>
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<tr>
<td>120</td>
<td>141 ± 12</td>
<td>41 ± 3</td>
<td>7.38 ± 0.06</td>
<td>72 ± 8</td>
<td>10.15 ± 3.41*</td>
<td>3.34 ± 1.42*</td>
<td>0.32 ± 0.04†</td>
</tr>
</tbody>
</table>

All data are presented as mean ± SD. $P_{gO_2}$, $P_{gCO_2}$, pH, and plasma glucose are from arterial samples. MAP = mean arterial pressure; Glbr/Gpl = 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 Glpl data. The relationship of Glpl to Glbr, again in all rats, was also examined. There was a close relationship between plasma and Glbr concentrations ($r = 0.95; P < 0.0001$ by t test). This relationship can be described by the formula: Glbr = 0.35 × Glpl − 0.65, where Glbr is expressed as micromoles per gram and Glpl is expressed as micromoles per milliliter.

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

As expected, the untreated diabetic control rats had a significantly greater Glpl (24.99 ± 1.61 µmol·mL$^{-1}$) and Glbr (8.11 ± 1.09 µmol·g$^{-1}$) than did the untreated nondiabetic rats ($P < 0.0001$ and $P < 0.001$, respectively) (table 1). Furthermore, Glbr/Glpl was significantly greater in diabetic control rats (0.32 ± 0.04) than in nondiabetic

![Fig. 1](image1.png) 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](image2.png) 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.
control rats (0.25 ± 0.05; \( P < 0.001 \))(table 1). Saline treatment in the saline-treated diabetic group had no effect on \( \text{Gl}_{\text{br}} \), \( \text{Gl}_{\text{br}}/\text{Gl}_{\text{pl}} \) 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 \( \text{Gl}_{\text{pl}} \) decreased to normoglycemic levels (10.15 ± 3.41 \( \mu \text{mol} \cdot \text{ml}^{-1} \)) by 120 min (table 1 and fig. 1). The \( \text{Gl}_{\text{br}} \) at 120 min in these rats (3.54 ± 1.42 \( \mu \text{mol} \cdot \text{g}^{-1} \)) was significantly less than that of the diabetic control rats \( (P < 0.0001) \). Despite this insulin-induced reduction in \( \text{Gl}_{\text{br}} \), there was a strong tendency for the \( \text{Gl}_{\text{br}} \) concentration in the insulin-treated diabetic group at 120 min to differ from that of the non-diabetic saline-treated group at the same time period \( (P = 0.058) \)(table 1 and fig. 2). The \( \text{Gl}_{\text{br}}/\text{Gl}_{\text{pl}} \) 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 \( \text{Gl}_{\text{br}}/\text{Gl}_{\text{pl}} \) 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 or laboratory animals 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. During periods of hyperglycemia, glucose rapidly crosses the blood–brain barrier by facilitated diffusion and other secondary mechanisms, producing elevated \( \text{Gl}_{\text{br}} \). If the brain is exposed to ischemia, it will anaerobically metabolize the available glucose to lactic acid. 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, although this issue is controversial.

Clinically, if monitoring of glucose is desired, we cannot measure \( \text{Gl}_{\text{br}} \), but rather we measure \( \text{Gl}_{\text{pl}} \) and assume there is a correlation between these variables and \( \text{Gl}_{\text{br}} \). Studies have shown that as \( \text{Gl}_{\text{br}} \) or \( \text{Gl}_{\text{pl}} \) increases, the \( \text{Gl}_{\text{br}} \) also increases. Similarly, when \( \text{Gl}_{\text{br}} \) or \( \text{Gl}_{\text{pl}} \) decreases under the influence of insulin, the \( \text{Gl}_{\text{br}} \) also tends to decrease. Our data support these conclusions but additionally demonstrate that for a given \( \text{Gl}_{\text{pl}} \), 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 \( \text{Gl}_{\text{br}} \) and \( \text{Gl}_{\text{pl}} \) 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, noted an accumulation of glucose in the brains of insulin-treated diabetic rats when normoglycemia was obtained after 0.5 h of insulin treatment. In addition, in three pilot rats, glucose accumulation in the brain was observed if insulin therapy, and thus normoglycemia, continued for 18–24 h. This suggests that a failure to attain equilibrium between \( \text{Gl}_{\text{br}} \) and \( \text{Gl}_{\text{pl}} \) during rapid glucose fluxes was not the cause of the glucose accumulation in our study or that of Pelligrino et al.

A failure of \( \text{Gl}_{\text{br}} \) and \( \text{Gl}_{\text{pl}} \) concentrations to reach equilibrium can occur in the rat during periods of rapidly decreasing \( \text{Gl}_{\text{br}} \), as recently demonstrated by Weglinski and Lanier. 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. When this lack of equilibrium occurs, it is manifested as an alteration in \( \text{Gl}_{\text{br}}/\text{Gl}_{\text{pl}} \). In the present study, the \( \text{Gl}_{\text{br}}/\text{Gl}_{\text{pl}} \) did not change with insulin infusion in diabetic rats, and \( \text{Gl}_{\text{br}}/\text{Gl}_{\text{pl}} \) did not differ between insulin- and saline-treated diabetic rats. The latter observation suggests that insulin infusion per se was not responsible for \( \text{Gl}_{\text{br}} \) accumulation in diabetic rats. Finally, follow-up studies in our laboratory have evaluated the relationship between \( \text{Gl}_{\text{br}} \) and \( \text{Gl}_{\text{pl}} \) in biologically bred diabetic rats and compared those results to saline-treated biologically bred nondiabetic litter mates. The results...
of these studies confirm our results in streptozocin-treated diabetic rats and additionally rule out streptozocin treatment as the cause of Glbr 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. 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, for a given degree of brain ischemia there is a correlation between Glbr and the severity of the postischemic neurologic injury. By reducing Glbr concentrations in hyperglycemic patients to values found in normoglycemic patients, it may be possible to reduce ischemic brain injury. However, if one monitors Glbr or Glbr during restoration of normoglycemia, and those values underestimate the Glbr 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 Glbr and ischemic neurologic injury in subjects studied after transient glucose infusions. In the latter setting, Glbr declined faster than Glbr, and thus, underestimated Glbr.

In the present study, some of the saline-treated diabetic rats had significantly lower arterial blood pH values than did nondiabetic rats treated with saline for the same duration (table 1). This pH reduction was due probably to slight ketoadidosis 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, 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. Based on existing data, it is unlikely that the rapid reduction in Glbr 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 Glbr in chronically diabetic subjects may result in a state of cerebral hypermetabolism, a condition that in itself may have an adverse effect on the ischemic brain. Third, our data suggest that the acute restoration of normal Glbr or Gp in chronically diabetic subjects may not result in a complete restoration of a normal Glbr. 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 Glbr 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 Glbr and Gbr 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. Recently, it has been reported that there is actually an increase in activity of the blood–brain barrier glucose transporter and that this phenomenon may be linked to a change in mRNA activity. Nonetheless, regardless of the mechanism, the present study reveals that insulin-treated diabetic subjects have an increased Glbr/Gp 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 Glbr, we conclude that the measurement of Glbr or Gp in acutely insulin-treated, normoglycemic diabetics will underestimate both the Gbr and the degree of postischemic neurologic injury.

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