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Insulin Treatment of Corticosteroid-associated Hyperglycemia and Its Effect on Outcome after Forebrain Ischemia in Rats

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Background: **Recent studies have reported that dexamethasone worsens neuronal injury after brain ischemia. This effect is assumed to be secondary to drug-induced hyperglycemia. The current study used a rat model to test the hypotheses that insulin treatment of dexamethasone-induced hyperglycemia would result in a postischemic neurologic outcome that is: (1) better than that of hyperglycemic, dexamethasone-treated subjects; and (2) better than, or equal to, that of saline-treated control subjects.**

Methods: **Twenty-four halothane-anesthetized (1.0% inspired) rats were randomly assigned to one of three treatment groups (N = 8 in each group): (1) normoglycemic, placebo-treated rats (group P) received an intravenous saline infusion; (2) hyperglycemic, dexamethasone-treated rats (group D) received 2 mg/kg intraperitoneal dexamethasone at 2 days, 1 day, and 3 h before ischemia plus an intravenous saline infusion; and (3) normoglycemic, dexamethasone- and insulin-treated rats (group DI) received the same treatment as group D, plus an intravenous insulin infusion shortly before ischemia. Blood gases and acid-base status were maintained within normal physiologic ranges. Pericranial and rectal temperatures were maintained at normothermia. Forebrain ischemia of 10 min duration was produced using an established model. Neurologic function was assessed by a blinded observer at 24 and 48 h postischemia. Brain histopathology was assessed at the time of ischemia-related death or after the examination at 48 h. All 24 rats were included in the analysis of neurologic function; however, only 21 rats that survived for ≥24 h postischemia were included in the histologic analysis.**

Results: **Rats were well matched for systemic physiologic variables, with the exception of glucose concentrations. Plasma glucose concentration immediately before ischemia was as follows: group P = 129 ± 8 mg/dl (mean ± SD), group D = 344 ± 29 mg/dl, and group DI = 123 ± 17 mg/dl. At 48 h postischemia, groups P and DI were minimally injured and had similar functional scores. In contrast, all group D rats died of cerebral ischemia. Histologic injury was significantly worse in group D than in either group P or DI, but did not differ significantly between groups P and DI. When all groups were combined, there was a significant correlation between neurologic function and total histopathology score ranks.**

Conclusions: **In the current study, dexamethasone administration before brain ischemia resulted in a worsening of postischemic outcome that was related to drug-induced hyperglycemia. Restoration of normoglycemia, using insulin, resulted in a functional outcome similar to that in group P, and an attenuation of dexamethasone-associated histologic injury. (Key words: Complications, ischemia: brain. Corticosteroids: dexamethasone. Blood: glucose concentration. Outcomes: neurologic.)**

CORTICOSTEROID medications, including dexamethasone, are used extensively in the treatment of neurosurgical and neurointensive care patients. Despite their widespread use, there are few situations in which corticosteroids have been proven to benefit acute neurologic function or long-term outcome. Laboratory and clinical studies have shown that corticosteroid drugs: (1) are effective in reducing vasogenic cerebral edema and intracranial pressure in patients with brain neoplasms or abscesses, (2) improve neurologic function in patients with pseudotumor cerebri, and (3) improve both sensory and motor function when administered within 8 h of spinal cord injury.[1–7]

In contrast, studies evaluating the effectiveness of corticosteroids in the setting of head injury,[8–11] or global[12–15] or focal brain ischemia,[2,16–20] have demonstrated either no improvement or a worsening of neurologic outcome.

The current study employed a rat model of forebrain ischemia to test three hypotheses: (1) dexamethasone

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worsens both functional and histologic evidence of ischemic brain injury, (2) increased ischemic injury is related to dexamethasone-induced hyperglycemia, and (3) insulin treatment of hyperglycemia, in dexamethasone-treated subjects, will result in an outcome that is better than, or equal to, that of placebo-treated subjects.

Materials and Methods

Preischemic Preparation

After Institutional Animal Care and Use Committee approval, the study was conducted under aseptic conditions, using 26 male Sprague Dawley rats weighing 260–365 g. The rats were fasted for 10–12 h before study, but had free access to water. On the morning of surgery, anesthesia was induced with 4% halothane inspired in oxygen, in a methyl methacrylate polymer induction box. Once anesthetized, the trachea was intubated using a 14-G polytetrafluorethylene catheter, and the lungs were mechanically ventilated. A tidal volume of 3.5 ml was used, and the respiratory rate and inspired oxygen fraction (balance nitrogen) were adjusted to maintain Pa_{CO_2} at 38 ± 2 mmHg (mean ± range) and Pa_{O_2} at 150 ± 25 mmHg (IL electrodes at 37°C; Lexington, MA). Anesthesia was maintained with 1.0–2.0% halothane inspired in oxygen and nitrogen during the preparatory period; thereafter, halothane was maintained at 1% inspired in all rats for at least 10 min before brain ischemia. Neuromuscular block was induced and maintained with 0.3–0.4 mg intravenous pancuronium.

A bifrontal electroencephalogram was monitored using periosteal needle electrodes and a polygraph (Grass Instruments, Quincy, MA). Pericranial temperature was monitored using needle thermistors inserted beneath the temporalis muscles bilaterally, and core temperature was assessed using a rectal thermistor (YSI, Yellow Springs, OH). Temperatures were maintained at 37.0 ± 0.2°C using overhead heating lamps and a ventral heating pad. Cannulas were inserted into the left femoral artery and vein using PE-50 polyethylene catheters (Becton Dickinson, Parsippany, NJ).

The animals were prepared for the production of transient, forebrain ischemia.[21] Through a neck incision, the carotid arteries were identified and, using pliable PE-10 polyethylene tubing, isolated. Thereafter, a silastic cannula (OD = 2.2 mm) was inserted *via* the right jugular vein into the superior vena cava, and the rats were given 50 units intravenous heparin. The superior vena caval catheter and isolated carotid arteries were subsequently used in the production of cerebral ischemia.

Rats were randomly assigned to one of three study groups. Normoglycemic, placebo-treated rats (group P; N = 9) received an infusion of 0.9% saline solution at a rate of 0.67 ml/h intravenously during the preparation period. Hyperglycemic, dexamethasone-treated rats (group D; N = 8) received 2 mg/kg intraperitoneal dexamethasone at 2 days, 1 day, and 3 h before the onset of cerebral ischemia. This regimen is similar to that described by Koide *et al.*,[22] who studied the effect of dexamethasone on histologic outcome after forebrain ischemia. Group D rats also received the same saline infusion as group P rats. Normoglycemic, dexamethasone- plus insulin-treated rats (group DI; N = 9) received the same dexamethasone regimen as that described for group D rats; however, they also received the aforementioned saline solution to which regular bovine/porcine insulin (Eli Lilly, Indianapolis, IN) was added to produce a concentration of 1.5 units/ml. The insulin solution was infused at a rate of 0.67 ml/h (*i.e.*, 1.0 unit/h) until normoglycemia was achieved. The study was designed so that the study durations and intravenous infusions were similar among groups.

Production of Ischemia

In all rats, fluid infusions (including insulin) were discontinued immediately before the onset of ischemia. Ischemia was induced using the forebrain ischemia model described previously by Smith *et al.*[21] Briefly, the mean arterial blood pressure (MAP) was reduced to 43 ± 3 mmHg using a combination of 0.5–1.0 mg intravenous trimethaphan and jugular venous phlebotomy. Immediately thereafter, blood flow through both carotid arteries was interrupted using removable surgical aneurysm clips. Ischemia was confirmed by the onset of an isoelectric electroencephalogram. At the onset of ischemia, halothane and nitrogen were discontinued. Throughout the ischemic period, MAP was maintained at 43 ± 3 mmHg using jugular blood withdrawal or infusion. At the completion of the 10 min ischemic period, cerebral circulation was restored, within 1 min, by removing the carotid occlusion clips and restoring MAP to ≥90 mmHg by reinfusing blood withdrawn previously. Additionally, 0.5 mEq intravenous sodium bicarbonate was administered on reperfusion.

Postischemic Treatment

Mean arterial pressure was maintained at 90–150 mmHg using jugular blood withdrawal or infusion as needed. All temperatures were maintained at 37 ± 0.2°C during the initial 30 min postischemia. Lungs were mechanically ventilated and sedation was provided with 50% nitrous oxide in oxygen. Before decannulating the femoral vein, all previously withdrawn blood was reinfused. At 1 h postischemia, neuromuscular block was reversed with 0.07 mg/kg neostigmine and 0.012 mg/kg intraperitoneal glycopyrrolate, nitrous oxide was discontinued, and animals were weaned from the mechanical ventilator. After demonstrating normal spontaneous ventilation, the trachea was extubated. Rats were then placed in an observation cage for the subsequent 48 h. During this period, the rats were examined every 2–9 h, and progress notes were recorded.

Assessment of Neurologic Function

Neurologic function was assessed at 24 and 48 h postischemia, by an observer (JTB) blinded to the treatment groups. Function was quantified using the 50-point scoring scale of LeMay *et al.*[23] Briefly, a total neurologic deficit score was derived for each rat based on the sum scores of five categories. These categories included: (1) level of consciousness (deficit score range: 0–10 points), (2) motor function (0–17 points), (3) respiratory effort (0–9 points), (4) cranial nerve function (0–8 points), and (5) spinal nerve function (0–6 points). A score of ≤8 denoted normal function, whereas a score of 50 indicated death.

Assessment of Histologic Injury

After the neurologic examination at 48 h, surviving rats were anesthetized with halothane and their brains were preserved *in situ*. Briefly, a left thoracotomy was performed to expose the great vessels. Then, in rapid succession, the descending aorta was isolated and clamped distal to the left common carotid artery, a right atriotomy was performed, and 0.9% saline solution was infused through a 20-G needle inserted into the descending aorta proximal to the aortic cross-clamp. A total of 25 ml of 0.9% saline solution, followed by 25 ml 4% buffered paraformaldehyde, was infused. The brains were removed and stored for a minimum of 4 weeks, the first two in 4% buffered paraformaldehyde, the remainder in 10% formalin solution. Thereafter, whole-mount, paraffin-embedded microsections were cut to 6 μm thickness and stained with hematoxylin and eosin.[24] Histologic evaluation was performed by a neuropathologist (BWS) blinded to the treatment groups. Histopathology was graded according to a previously described scale.[24] Severity of injury was assigned points, bilaterally, according to the following scale: normal, 0; minimal, 1; moderate, 2; severe, 3; and maximal, 4. The points were then multiplied by a weighting factor (infarction, 4×; ischemic nerve cell change, 2×; edema, 1×) to obtain a score for each of 16 brain regions. The analysis for one of these regions, the hippocampus, was further subdivided to provide an assessment of the CA1, CA2, and CA3,4 segments. The hippocampus was chosen for segmental analysis because of previous reports of regional (CA1) selectivity of neuronal injury in this model.[25] The scores of individual brain regions, as well as a total score for all regions, were statistically compared among treatment groups. A separate analysis was performed to compare injury within the hippocampal segments.

Exclusion Criteria

Animals that did not meet all preestablished protocol criteria were excluded from data analysis. Exclusion was based on strict criteria: rats in either of the dexamethasone-treated groups not having a blood glucose concentration ≥ 180 mg/dl before study intervention; not achieving forebrain ischemia for 10 min; the appearance of postischemic MAP < 90 mmHg or > 150 mmHg for more than 1 min, or a MAP < 50 mmHg at any time; or systemic compromise or death from a cause other than ischemic neurologic injury (*i.e.*, airway obstruction, rodent respiratory virus-induced pneumonia, pulmonary edema, or cerebral hemorrhage). All decisions to exclude a rat from the final data analysis were made by the blinded referee (WLL).

Previous studies have shown that postischemic histologic changes in the brain require 24 h or more to mature.[26] Thus, any rat that died from ischemia within 24 h of the ischemic insult was not included in the histologic data analysis, but was included in the analysis of neurologic function, provided the study criteria had been fulfilled. If the rat died after 24 h but before the 48-h observation and data acquisition period, the brain was excised and preserved, and histologic data from the rat were included in the final statistical analysis. In all cases, the cause of death was determined by extensive necropsy.

Statistical Analysis

Physiologic variables were analyzed and compared among groups using a one-way analysis of variance and

Table 1. Physiologic Variables

Variables	Group P (placebo)		Group D (dexamethasone)		Group DI (Dexamethasone and insulin)	
	Preischemia	10 min postischemia	Preischemia	10 min postischemia	Preischemia	10 min Postischemia
Pa_{O_2} (mmHg)	159 ± 7	159 ± 16	162 ± 8	156 ± 15	162 ± 9	148 ± 16
Pa_{CO_2} (mmHg)	38 ± 1	43 ± 3	37 ± 2	42 ± 5	38 ± 1	43 ± 3
*p*H	7.35 ± 0.01	7.33 ± 0.03	7.37 ± 0.02*	7.35 ± 0.04	7.37 ± 0.02*	7.35 ± 0.02
Hematocrit	43 ± 2	40 ± 2	42 ± 2	37 ± 2	42 ± 3	40 ± 3
MAP (mmHg)	99 ± 14	146 ± 9	101 ± 16	146 ± 11	95 ± 23	153 ± 6
Pericranial temperature (°C)	37.0 ± 0.0	37.0 ± 0.1	37.0 ± 0.0	37.0 ± 0.1	37.0 ± 0.1	37.0 ± 0.1
Plasma glucose (mg/dl)	129 ± 8	151 ± 13	344 ± 29*	465 ± 71*	123 ± 17†	161 ± 52†

Values are mean ± SD (n = 8 per group). The pericranial temperature was derived by averaging the right and left subtemporalis measurements.

MAP = mean arterial blood pressure.

* $P < 0.05$ *versus* group P.

† $P < 0.05$ *versus* group D.

post hoc F tests. Neurologic function and histology scores were compared using the Kruskal-Wallis test and a Bonferroni's correction of the rank sum test. The Spearman rank correlation coefficient was used to test for an association between neurologic function and histology scores. $P < 0.05$ was considered significant.

Results

Physiologic Variables

The three treatment groups were well matched for preischemic and postischemic physiologic variables, with the exception of blood glucose concentrations. Plasma glucose concentration immediately before ischemia was as follows: group P = 129 ± 8 mg/dl (mean ± SD), group D = 344 ± 29 mg/dl, and group DI = 123 ± 17 mg/dl ($P < 0.001$ for D *vs.* P or DI; P = 0.6 for P *vs.* DI; table 1). In each group, the duration of fluid infusion before ischemia was 19 ± 6 min.

Exclusions

Two animals (1 rat in group P and 1 in group DI) were entirely excluded from the study because of partial airway obstruction after extubation (*i.e.*, postintubation croup). Neither animal had evidence of unusual neurologic findings before death. After their deaths at 22 h and 24 h, respectively, necroscopic examination revealed mucosal edema of the glottic and subglottic structures.

Additionally, three rats in group D died from cerebral ischemia before 24 h postischemia. Based on preestablished criteria, they were excluded from histologic assessment, but were included in the evaluation of neurologic function.

Functional Outcome

Twenty-four rats were included in the analysis of functional outcome (fig. 1). At 48 h postischemia, group P and DI rats were minimally injured and had

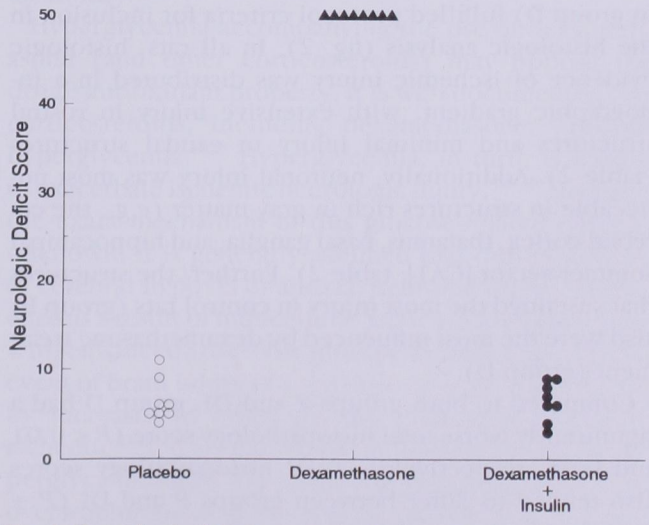

Fig. 1. Neurologic deficit scores at 48 h postischemia. A score of ≤8 points denotes normal function, whereas a score of 50 denotes death. Normoglycemic placebo-treated and dexamethasone plus insulin-treated rats (*i.e.*, groups P and group DI, respectively) were minimally injured and had similar functional outcome scores ($P > 0.9$). In contrast, all hyperglycemic, dexamethasone-treated rats (*i.e.*, group D) died from cerebral ischemia ($P < 0.001$ *vs.* groups P or DI).

similar functional outcome scores (*i.e.*, they received median neurologic deficit scores of 6 [range: 4–11] and 7 [range: 3–9], respectively [$P > 0.9$]). Collectively, rats in these two groups were alert, groomed themselves, maintained sternal posturing, exhibited no ataxia or circling, and none experienced tonic-clonic seizure activity. Further, neurologic function scores in these two groups were indistinguishable from those of rats studied in our laboratory who were neither instrumented nor exposed to cerebral ischemia (median deficit score of 5; range: 1–8; unpublished data). In contrast, functional outcome in group D rats was significantly worse than that of groups P or DI ($P < 0.001$ for both). After ischemia, group D rats were stuporous and exhibited poor facial grooming (*i.e.*, they developed periorbital and perinasal porphyrin staining bilaterally). Similar to the findings of Smith *et al.*,[21] by 24 h postischemia, three group D rats had progressed through a series of hyperexcitability, crescendo tonic-clonic seizure activity, status epilepticus, and eventually neurogenic death (*i.e.*, a neurologic deficit score of 50). By 48 h postischemia, the remaining five group D rats had died, after progressing through the same pattern of deterioration noted earlier (fig. 1).

Histologic Outcome

Twenty-one rats (N = 8 for groups P and DI; N = 5 in group D) fulfilled protocol criteria for inclusion in the histologic analysis (fig. 2). In all rats, histologic evidence of ischemic injury was distributed in a topographic gradient, with extensive injury in rostral structures and minimal injury in caudal structures (table 2). Additionally, neuronal injury was most noticeable in structures rich in gray matter (*e.g.*, the cerebral cortex, thalamus, basal ganglia, and hippocampal Sommer sector [CA1]; table 2). Further, the structures that sustained the most injury in control rats (group P) also were the most influenced by dexamethasone treatment (group D).

Compared to both groups P and DI, group D had a significantly worse total histopathology score ($P < 0.01$ and 0.05, respectively). Total histopathology scores also tended to differ between groups P and DI ($P = 0.06$).

When data from all three groups were combined, there was a significant correlation between overall neurologic function and total histopathology score ranks (N = 21 pairs of data; $r_s = 0.71$; $P < 0.001$).

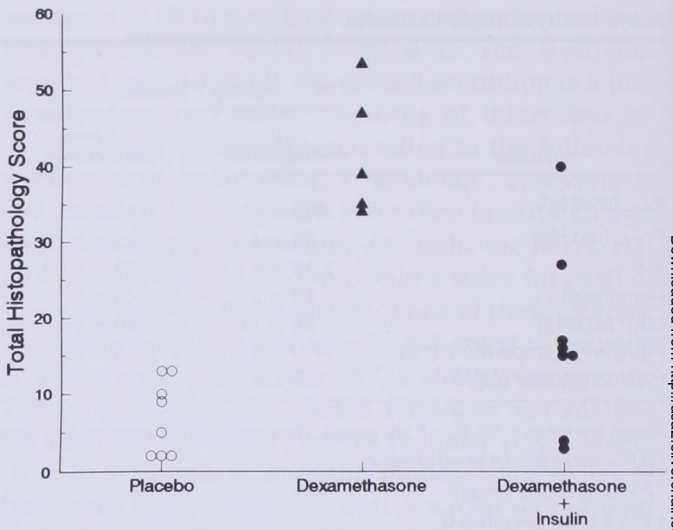

Fig. 2. Postischemic histologic scores in rats. A high score denotes extensive injury, whereas a low score denotes minimal injury. Total histopathology scores were significantly worse in hyperglycemic, dexamethasone-treated rats (*i.e.*, group D) than in either normoglycemic placebo-treated or dexamethasone plus insulin-treated rats (*i.e.*, groups P or DI; $P < 0.01$ or 0.05, respectively). There also was a tendency for scores to differ between groups P and DI ($P = 0.06$).

Discussion

Use of corticosteroid medications, including dexamethasone, has been widespread in neurosurgical and neurointensive care patients despite limited experimental evidence of their effectiveness. The reason for widespread corticosteroid use in these patients is probably secondary to the assumption that these medications may not do any harm, but perhaps may benefit the patient because of their antioxidant properties.[27,28] Consistent with this assumption, a recent survey by Craen *et al.*,[29] polling members of the Society of Neurosurgical Anesthesia and Critical Care, reported that 36% of the respondents who use specific brain protective therapies indicated they administered steroids during cerebral aneurysm clipping. This surgical procedure is reported to have a high incidence of new onset, postoperative neurologic deficits.[30]

Despite the common use of corticosteroids in neurologically injured patients, both animal and human studies have failed to demonstrate convincing improvement of neurologic outcome after cerebral ischemia or head injury. Specifically, Koide *et al.*[22] demonstrated, in a rat model of forebrain ischemia, that chronic pretreatment with dexamethasone resulted in a significant: (1) increase in preischemic blood and

Table 2. Regional Histopathology Scores

	Group P (placebo)		Group D (dexamethasone)		Group DI (dexamethasone and insulin)	
	Median	Range	Median	Range	Median	Range
Brain region						
Lateral septal nucleus	0	0–1	3	1–10*	1.5	0–3
Hippocampus	0.5	0–1	2	0–4	3	0–6*
Thalamus	0.5	0–2	6	0–8*	0.5	0–5
Enterorhinal cerebrum	0.5	0–2	3	2–4*	2	0–4
Occipital cerebrum	0.5	0–2	3	1–7*	2	0–4
Central cerebrum	0.5	0–2	8	3–14*	2	0–5†
Caudate-putamen	1	0–2	6	3–8*	2.5	0–5†
Frontal cerebrum	1.5	0–3	10	4–12*	2	0–6†
Total	7	2–13	39	34–53.5*	15.5	3–40†
Hippocampus segment						
CA1	0.5	0–2	3	0–4	3	0–8
CA2	0	0–2	2	0–4	2	0–5
CA3,4	1	0–1	1	0–3	2.5	0–4

Histopathology scores of specific brain regions, total brain, and hippocampus segments. The severity of injury was assigned points (*e.g.*, normal = 0; minimal = 1; moderate = 2; severe = 3; maximal = 4) bilaterally. The points were then multiplied by a weighting factor (*e.g.*, infarction = 4×; ischemia = 2×; edema = 1×) to obtain a score for each of the 16 brain regions. The bilateral scores were averaged to produce a single score for each brain region. The total score was calculated by adding the score of the 16 brain regions, including the hippocampus, but excluding the hippocampus segment scores. The anterior commissure, central white matter, cerebellar-Purkinje cells, corpus callosum, medulla, midbrain, pons, and substantia nigra received median histopathology scores of zero for all three study groups.

* $P < 0.05$ *versus* group P (using Bonferroni correction of rank-sum test).

† $P < 0.05$ *versus* group D (using Bonferroni correction of rank-sum test).

brain glucose concentrations, (2) worsening of intraneuronal lactic acidosis after ischemia, (3) increase in the incidence of seizures, and (4) worsening of histopathology after ischemia. However, neurologic function was not assessed in this study. In humans experiencing acute stroke, dexamethasone treatment resulted in either no improvement[16,17,19,20] or a worsening[18] of neurologic function and mortality. In a related study of head injured patients having increased intracranial pressure, Dearden *et al.*[8] reported that dexamethasone administration resulted in a higher incidence of primary brain death, when compared to placebo-treated patients. The latter was associated with a drug-induced hyperglycemia.

Theoretically, the effects of corticosteroids on the ischemic brain are determined by two independent, opposing characteristics: (1) an antioxidant effect, and (2) a hyperglycemia-inducing effect.[8,27,28,31] Because free radicals are believed to contribute to neuronal injury during and after cerebral ischemia, it would seem intuitively obvious that the antioxidant property[27,28] of corticosteroids should provide neuronal protection and improve neurologic outcome. Such beneficial properties have been reported with antioxidant steroids that are devoid of a hyperglycemia-inducing effect (*i.e.*, the lazaroids).[27,28]

Hyperglycemia accompanying the use of dexamethasone (and other corticosteroids) may oppose the drug's antioxidant property. It is well documented that corticosteroids, including dexamethasone, produce hyperglycemia.[8,27] Hyperglycemia, in turn, is known to exacerbate ischemic neurologic injury.[32–36] Although the exact mechanism of this glucose-related effect is unknown, it is generally assumed that during periods of cerebral hypoxia or anoxia, neuronal injury is worsened as a result of intracellular lactic acidosis associated with enhanced anaerobic glucose metabolism.[37] In the event of brain injury of a type known to be exacerbated by increases in brain glucose concentrations (*e.g.*, ischemic[18,22,32–36] and traumatic brain injury[8]), the hyperglycemia-inducing effect of corticosteroids may overwhelm the potential antioxidant benefit, resulting in a net detriment to the ischemic brain.

When given to previously hyperglycemic patients, insulin therapy results in acute, and parallel, reductions in both blood and brain glucose concentrations.[38,39] In laboratory animals, insulin has been reported to improve postischemic neurologic outcome when admin-

istered to: restore normoglycemia in previously hyperglycemic subjects,[25] induce mild hypoglycemia in previously normoglycemic subjects,[23] or maintain normoglycemia in subjects receiving a concomitant glucose infusion.[40]

Restoring normoglycemia, using acute insulin therapy in chronically hyperglycemic subjects (streptozotocin-induced diabetes mellitus of 1 week duration), resulted in an intraischemic cerebral lactic acidosis (forebrain ischemia model) that was similar to chronically normoglycemic subjects.# A decrease in intraneuronal acidosis, associated with restoring normoglycemia, may be the mechanism responsible for improving postischemic neurologic outcome. Additionally, recent research suggests that insulin may have a beneficial effect on the ischemic brain that is independent of glucose concentrations.[40–44] Although the exact mechanism of this phenomenon has not been elucidated, the proposed mechanisms include: an insulin receptor-mediated inhibition of neurotransmission within the brain,[40–42] an insulin-mediated inhibition of platelet aggregation at the site of microvascular injury,[43] and stimulation of an insulinlike growth factor (somatomedin-C) receptor in the brain.[40,42,44]

Thus, in the setting of our study, the acute administration of insulin might be expected to reverse the potentially detrimental effects of hyperglycemia, and unmask any glucose-independent beneficial effects of dexamethasone or insulin.

In the current study, insulin administration appeared to completely reverse the dexamethasone-related effect on neurologic function, but only attenuated the histologic injury. Our results suggest that dexamethasone-exacerbation of ischemic neurologic injury is related to glucose concentrations, and the detrimental effects of hyperglycemia overwhelm any potentially beneficial property of the corticosteroid, including antioxidant effects.

It is generally assumed that only hyperglycemia at the time of, not after, ischemia is important in modulating outcome after brain ischemia.[34,45] Because worsening of neurologic outcome after dexamethasone treatment appears primarily to be a glucose-related response, it follows that dexamethasone administration after brain ischemia would probably not result in a worsening of neurologic outcome. However, patients at risk for ongoing or recurrent brain ischemia would likely be adversely affected by dexamethasone-mediated hyperglycemia.

In summary, our study demonstrated that: (1) chronic dexamethasone administration before transient, forebrain ischemia resulted in a significant worsening of both neurologic functional and histologic outcomes when compared to normoglycemic control rats (group P); (2) the worsening of neurologic outcome in dexamethasone-treated rats was related to an increase in the blood glucose concentration; and (3) the restoration of normoglycemia using insulin resulted in a functional outcome indistinguishable from that of control rats, and an attenuation of dexamethasone-associated histologic injury. Our study did not identify any beneficial effects of dexamethasone, including an antioxidant effect, that have been hypothesized by others.[27,28]

Assuming that our results in rats are transferable to humans, we recommend monitoring and controlling blood glucose concentrations in dexamethasone-treated patients who are at risk for ischemic neurologic injury.

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