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Hyperglycemia Exacerbates and Insulin Fails to Protect in Acute Renal Ischemia in the Rat

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Hyperglycemia worsens ischemic injury in several ischemic models. To determine whether renal lactate accumulation was associated with hyperglycemia-exacerbated postischemic renal dysfunction and mortality, halothane-anesthetized rats underwent right nephrectomy and 45 min of left renal artery and vein occlusion. Prior to ischemia, rats received saline (n = 22), glucose (2 g/kg, n = 22), or insulin (4 U/kg, n = 18). Sham-operated glucose-treated rats (2 g/kg, n = 4) underwent right nephrectomy and no vascular occlusion. As anticipated, glucose pretreatment elevated plasma glucose, while insulin pretreatment lowered plasma glucose; both were significantly different from values in saline controls. Creatinine was unchanged in sham-operated rats but was significantly higher in glucose-treated rats at 24 and 48 hr postischemia compared to saline controls. No statistical differences in creatinine were found when comparing saline controls to insulin-treated rats. Eighteen percent of glucose-treated rats survived to 72 hr postocclusion, while 45% of insulin-treated rats, 73% of saline control rats, and 100% of sham-operated rats survived this period. In a separate but identical treatment protocol, renal tissue was serially sampled and lactate content was determined in rats pretreated with saline (n = 7), glucose (n = 6) or insulin (n = 6) or sham-operated (n = 2) and receiving identical operation. Tissue lactate concentration did not change during serial sampling in the sham group. During ischemia, lactate was significantly higher in glucose-treated rats and significantly lower in insulin-treated rats as compared to saline controls. The adverse effects of exogenous glucose and attendant hyperglycemia on renal function during normothermic renal ischemia are demonstrated. Increased anaerobic metabolism of glucose with marked lactate accumulation may increase the severity of injury. However, a direct link between tissue lactate and ischemic damage is not fully supported since insulin reduced renal lactate but failed to lessen morbidity and mortality.

INTRODUCTION

Renal ischemia predictably accompanies a number of common operations, including renal transplantation and complex aortic reconstructions, and continues to contribute significantly to postoperative acute renal failure with high attendant mortality [1–4]. The pathophysiologic processes that lead to renal tubular cell death and epithelial disruption, however, remain poorly understood.

Recent experimental work has focused on the influence of metabolic substrate provision in the ischemic tissue. Numerous animal and clinical studies have shown that hyperglycemia in the setting of ischemia will enhance ischemic damage [5–28]. These investigations have focused primarily on hyperglycemia-exacerbated morbidity and mortality in acute cerebral ischemia. However, a recent demonstration of adverse consequences from exogenous glucose provision in renal ischemia in dogs suggests the need for further study of hyperglycemia-exacerbation of noncentral nervous system tissue injury [29].

The most widely hypothesized mechanism of hyperglycemia-exacerbated ischemic injury holds that during ischemia the cell undergoes rapid depletion of high energy stores and a shift from aerobic to anaerobic glycolysis with accumulation of its end product, lactate. Intracellular lactate accumulates, contributing to secondary compromise of cellular function [8, 14, 25–27]. We explored these initial alterations in carbohydrate metabolism in a rat model of normothermic renal ischemia. Two hypotheses were proposed: (1) hyperglycemia with increased metabolism of glucose to lactate exacerbates renal ischemic damage, and (2) insulin-induced reduction of glucose availability with limited lactate accumulation will ameliorate damage.

METHODS

Two discrete protocols were utilized. They were identical in every respect except that in the first functional endpoints and survival were assessed over a 72-hr postischemia period, while the second utilized tissue biopsy for lactate assay. The use of two protocols obviates any concern that the multiple biopsies influenced functional outcomes. All procedures were approved by and followed the guidelines of the Unit for Laboratory Animal Medicine (ULAM) of The University of Michigan Medical School.

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Functional protocol. Adult male Sprague–Dawley rats, weighing 270–330 g, were individually housed with free access to standard rodent chow and water. Ambient temperature was 26–27°C and 12 hour light/dark cycles were preserved. Approximately half of the experimental animals were maintained in metabolic cages. Following a 24- to 36-hr acclimation period, a 24-hr baseline urine output was determined. Baseline plasma glucose and creatinine concentrations were determined spectrophotometrically (Ames Seralyzer) prior to halothane anesthesia (or prior to insulin pretreatment).

Rats were randomly assigned to one of four treatment groups. Treatment solutions were administered by intraperitoneal (ip) injection immediately after anesthetic induction. Glucose-treated animals (n = 22) received an isoosmotic solution (2 g/kg). Ischemic control animals (n = 22) received saline (isovolumetric to the glucose-treated group). A third group (n = 18) received insulin (Lilly), 4 U/kg, by subcutaneous injection 45 min prior to anesthetic induction and isovolumetric saline after induction. Sham-operated (nonischemic) controls (n = 4) received 2 g/kg glucose, underwent the surgical and recovery procedures described below, but received no renal pedicle occlusion.

Anesthesia (1.5% chamber induction; 0.75% mask maintenance) was used and normothermia (37°C) was maintained with a thermal pad and external heat sources and continuously monitored via a rectal probe. The kidneys were approached via bilateral flank incisions. Right nephrectomy was performed. The left renal artery and vein were isolated and encircled with a snare of polyethylene tubing (PE 10 in a sheath of PE 160) tunnelled to dorsal midline and brought out through a stab wound. The snare was tightened and secured for 45 min and the animals were allowed to awaken. The polyethylene snare permitted occlusion and release in the awake animal with reliable reperfusion. (In the first experiments utilizing this modification, snare release and confirmation of reperfusion were performed under direct vision during a second brief period of halothane anesthesia. Doppler ultrasound confirmation of reperfusion was also obtained.) Animals were recovered with free access to food and water for 72 hr after occlusion.

During the recovery period, plasma glucose was determined at 4 hr and plasma creatinine was measured at 24, 48, and 72 hr postischemia. Urine was collected at 24-hr intervals. Urine osmolarity was determined daily (Roebling Osmometer). Animals surviving the 72-hr recovery period were evaluated under anesthesia to again verify reperfusion and then euthanized by halothane overdose. Postmortem examinations were performed on all animals that died prior to 72 hr.

Biopsy protocol. In a separate experiment, renal tissue was obtained for lactate analysis from animals assigned to the described treatment groups. A pneumatic biopsy drill with a 3-mm bore (Alko Diagnostic Corp.) provide quick tissue removal in conjunction with immediate freezing [30]. The operation described previously was utilized except the right kidney was approached first. A baseline tissue sample was obtained from the right kidney followed by immediate nephrectomy. Renal tissue (50–75 mg) from the left kidney at the corticomedullary junction at the midupper and midlower poles was obtained at 20 and 45 min of ischemia. Following snare release, reperfusion was again confirmed visually and by Doppler ultrasound. Tissue samples were kept in liquid nitrogen until being ground to a fine powder at −20°C and then transferred to 1 ml of 3 M perchloric acid. After adding 2 ml distilled water, the samples were centrifuged at 6750g and 4°C for 25 min. The supernatant was stored at −70°C until fluorometric lactate analysis with lactate dehydrogenase in a NAD-to-NADH-linked reaction [31].

Statistical methods. Baseline within-group values were compared to values obtained during the 72-hr observation period by paired t test. Baseline between-group comparisons of temperature, plasma glucose, and urine output were evaluated with one-way analysis of variance (ANOVA, $\alpha = 0.05$). Comparisons of the means of saline control versus insulin-treated and saline control versus glucose-treated groups were performed with the Student's t test with the Bonferroni correction for multiple comparisons [32]. All average values are expressed as means ± 1 standard error. Survival data for glucose-treated and insulin-treated animals were evaluated against saline ischemic controls using the Fisher's exact test and the Breslow survival curve analysis [33].

RESULTS

In the results that follow, comparisons were performed within each of the four treatment groups and between the saline and insulin- or glucose-treated groups.

Functional protocol. Comparison of the means of baseline variables (body weight, rectal temperature, plasma glucose, and urine output) by ANOVA or Student's t with Bonferroni correction revealed no statistically significant differences between the treatment groups (Table 1), except saline-treated rats weighed more than sham-operated rats. Significant ($P < 0.05$) postsurgical weight loss occurred in all groups; however, the treatment groups did not differ with respect to the degree of weight loss. Surgical manipulation alone caused a significant elevation in plasma glucose (Fig. 1). Glucose administration significantly augmented this hyperglycemic response. Insulin administration reduced preocclusion plasma glucose levels to 77 ± 3 mg/dl, significantly lower than preocclusion levels in the saline controls. Plasma glucose concentrations in sham-operated, glucose-treated rats were identical to levels achieved in glucose-treated rats undergoing renal pedicle occlusion. By 4 hr postocclusion, there was no difference in plasma glucose concentrations between saline and glucose- or insulin-treated groups (saline, 123 ± 4 mg/dl; glucose, 124 ± 3 mg/dl; insulin, 105 ± 6 mg/dl; sham, 135 ± 8 mg/dl).

TABLE 1

Baseline Variables: Recovery Protocol

	Saline (n = 22)	Glucose (n = 22)	Insulin (n = 18)	Sham (n = 4)
Body weight (g)	317 ± 3	308 ± 3	308 ± 3	293 ± 8*
Rectal temperature (°C)	36.6 ± 0.1	36.5 ± 0.1	36.5 ± 0.1	36.5 ± 0
Plasma glucose (mg/dl)	128 ± 3	129 ± 2	131 ± 3	142 ± 2
Urine output (ml/kg/day)	43 $\pm 7^{12}$	64 $\pm 10^{8}$	46 $\pm 8^{10}$	24 $\pm 3^{2}$

Note. Values are means ± 1 SEM for presurgical body weight, plasma glucose, urine output, and prerenal vessel occlusion rectal temperature for the functional protocol. Sample sizes are 22 for saline control, 22 for glucose-treated, 18 for insulin-treated, and 4 for sham-operated, glucose-treated or as indicated by superscript. Comparison (ANOVA or Student's t test with Bonferroni correction) between saline and glucose or insulin treatment reveals no significant difference between these variables.

* Indicates a significant difference ($P < 0.05$ ANOVA) between saline-treated and sham-operated groups.

TABLE 2

Plasma Creatinine

	Treatment			
	Saline	Glucose	Insulin	Sham
Baseline	0.4 ± 0.04	0.4 ± 0.04	0.4 ± 0.04	0.5 ± 0.02
n	22	22	18	4
24 hr	4.7 ± 0.1	5.6 ± 0.2*	5.0 ± 0.2	0.8 ± 0.1
n	22	20	18	4
48 hr	6.1 ± 0.4	7.6 ± 0.3**	6.6 ± 0.5	0.5 ± 0.02
n	15	14	14	4
72 hr	5.5 ± 0.7	5.9 ± 1.2	4.8 ± 0.8	0.4 ± 0.05
n	16	4	8	4

Note. Values are means ± 1 SEM for plasma creatinine in mg/dl prior to renal pedicle occlusion (baseline) and at 24, 48, and 72 hr after occlusion for saline control, glucose-treated, insulin-treated, and sham groups.

* $P < 0.001$.

** $P < 0.012$ by Student's t test with Bonferroni correction.

Functional parameters, mean daily plasma creatinine and urine output, are shown in Table 2 and Fig. 2, respectively. Baseline plasma creatinine did not differ among the comparison groups. Unilateral nephrectomy alone (sham-operated) did not significantly elevate daily plasma creatinine. In contrast, 45 min of normothermic renal pedicle occlusion produced significant elevation in plasma creatinine in all ischemic groups ($P < 0.001$ by paired t analysis). At 24 and 48 hr, plasma creatinine was significantly higher in the glucose-treated group compared to saline controls. Plasma creatinine tended to be higher in insulin-treated animals as compared to saline controls, but this difference was not statistically significant.

A significantly increased urine output was noted in the saline control group at 48 and 72 hr ($P < 0.04$ by paired t analysis). In contrast, glucose-treated rats showed significant oliguria at 24 hr compared to baseline values and to the saline controls. At 48 hr, two of the five glucose-treated animals surviving were polyuric (128 and 95 ml/

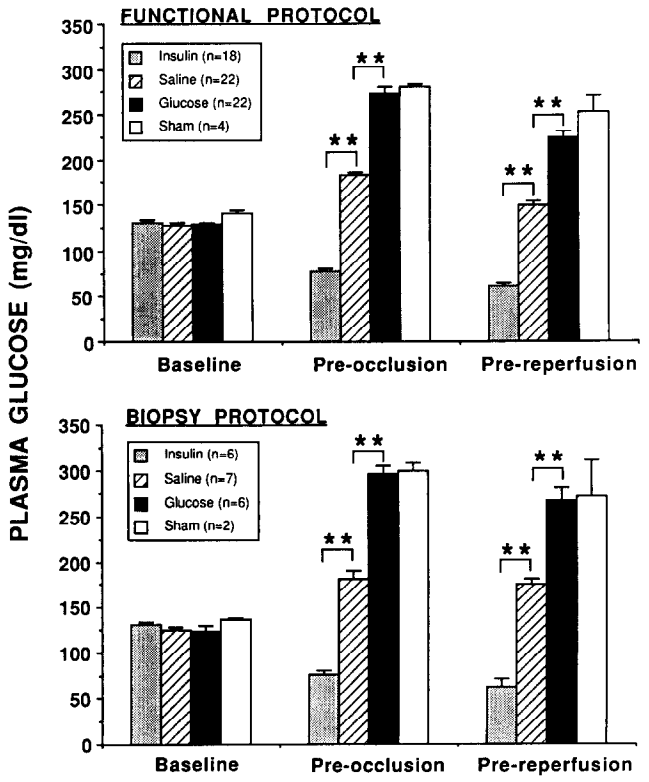

FIG. 1. Plasma glucose (mg/dl) at baseline (preanesthesia), preocclusion anesthetized, and prereperfusion (after 45 min of renal pedicle occlusion) time points in insulin-treated (4 U/kg); saline control, glucose-treated (2 g/kg); and sham-operated, glucose-treated (2 g/kg) rats. Top panel represents results from functional protocol; bottom panel, biopsy protocol. **$P < 0.001$ by Student's t test with Bonferroni correction. Sample sizes are indicated in the respective panel legends.

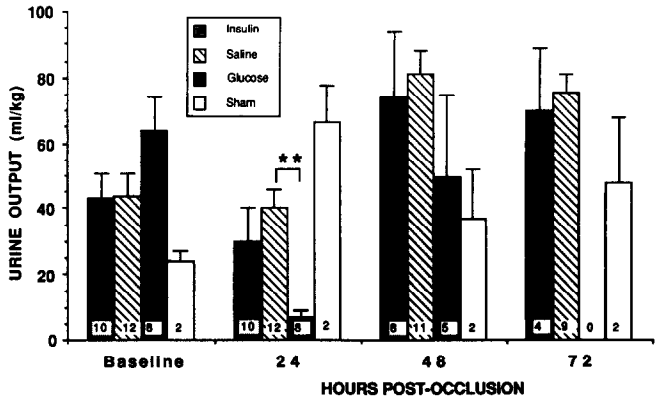

FIG. 2. Daily urine output at baseline and at 24, 48, and 72 hr postischemia in insulin-treated (4 U/kg); saline control, glucose-treated (2 g/kg); and sham-operated, glucose-treated (2 g/kg) rats. **$P < 0.012$ by Student's t test with Bonferroni correction. Sample sizes are indicated at the bottom of each bar.

kg), while the remaining three were oliguric (3, 4, and 24 ml/kg). Except for the most polyuric rat, 48-hr plasma creatinine exceeded 8.5 mg/dl in these glucose-treated rats, and only the most polyuric rat lived to 72 hr.

Baseline urine osmolarity did not differ among saline, glucose, and insulin groups. Values of 1442 ± 142, 1366 ± 113, 1549 ± 141, and 848 ± 190 mOsm/liter were obtained in the saline control (n = 7), glucose-treated (n = 8), insulin-treated (n = 9), and sham-operated groups (n = 2), respectively. All ischemic groups demonstrated significant reduction of concentrating ability postischemia ($P < 0.05$ by paired t analysis), while sham rats did not differ significantly from baseline. Concentrating ability was markedly reduced in the glucose-treated rats as compared to saline controls at 24 hr (384 ± 32 mOsm/liter vs 486 ± 18 mOsm/liter, $P < 0.05$). However, this difference failed to reach statistical significance at 48 hr (458 ± 26 mOsm/liter vs 537 ± 23 mOsm/liter, $P = 0.15$). Urine osmolarity was not different between insulin-treated and saline control rats at any postischemic time (451 ± 30 mOsm/liter at 24 hr, 514 ± 22 mOsm/liter at 48 hr, and 637 ± 87 mOsm/liter vs 668 ± 42 mOsm/liter at 72 hr).

Survival curves for 72 hr postocclusion are illustrated in Fig. 3. The sham-operated group showed no mortality. Glucose-treated animals had significantly greater mortality than saline controls ($P = 0.0003$ by Fisher's exact test, $P = 0.002$ by Breslow analysis). Insulin-treated animals also showed greater mortality at 72 hr as compared to saline controls by Fisher's exact test ($P = 0.05$); however, comparison using Breslow analysis revealed no significant difference in survival ($P = 0.44$).

Biopsy protocol. Comparison of the means of baseline variables (body weight, rectal temperature, plasma creatinine, plasma glucose, and tissue lactate) revealed no statistically significant differences between the treatment groups (Table 3). The alterations in plasma glucose produced in the functional protocol were reproduced in the biopsy protocol, seen in Fig. 1. The outcome measure was renal tissue lactate. Serial tissue biopsies did not alter renal tissue lactate in the sham-operated group (Fig. 4). However, after 20 min of renal pedicle occlusion, renal lactate accumulation rose significantly in all groups ($P < 0.005$ by paired t analysis). Renal lactate concentration was significantly lower in insulin-treated rats than saline controls at both 20 and 45 min after occlusion. Glucose pretreatment caused marked renal lactate accumulation with statistically higher values at 45 min of ischemia as compared to saline controls.

TABLE 3

Baseline Variables: Biopsy Protocol

	Saline (n = 7)	Glucose (n = 6)	Insulin (n = 6)	Sham (n = 2)
Body weight (g)	310 ± 11	319 ± 12	306 ± 7	331 ± 34
Rectal temperature (°C)	36.8 ± 0.1	36.7 ± 0.1	36.8 ± 0.2	37 ± 0
Plasma creatinine (mg/dl)	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.6 ± 0.1
Plasma glucose (mg/dl)	126 ± 3	124 ± 5	131 ± 3	137 ± 2
Tissue lactate (μmole/g)	1.0 ± 0.1	1.1 ± 0.1	0.8 ± 0.1	0.5 ± 0.1

Note. Values are means ± 1 SEM for presurgical body weight, plasma creatinine, plasma glucose, and preocclusion rectal temperature for the biopsy protocol. Sample sizes are seven for saline control, six for glucose-treated, six for insulin-treated, and two for sham-operated, glucose-treated. Comparison between saline and glucose or insulin treatment reveals no significant differences under these baseline conditions.

DISCUSSION

Renal ischemia continues to play a significant role in the pathogenesis of postoperative acute renal failure and attendant morbidity and mortality remain high. Understanding of cellular metabolic responses to ischemia re-

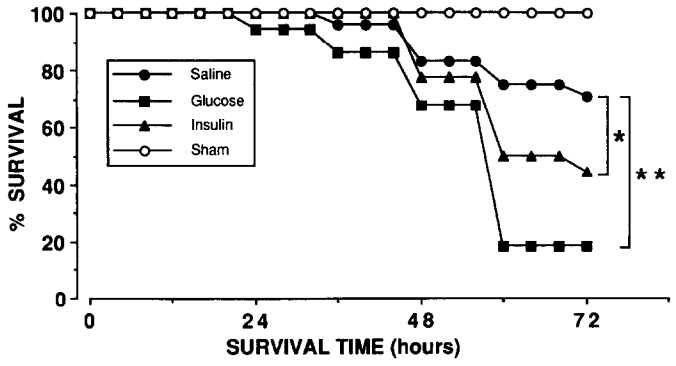

FIG. 3. Percentage survival for 72-hr recovery period following renal pedicle occlusion in insulin-treated (4 U/kg); saline control, glucose-treated (2 g/kg); and sham-operated, glucose-treated (2 g/kg) rats. Initial sample sizes are 22 for saline control, 22 for glucose-treated, 18 for insulin-treated, and 4 for sham-operated, glucose-treated. *P = 0.05 by Fisher's exact test and P = 0.44 by Breslow analysis; **P = 0.0003 by Fisher's exact test and P = 0.002 by Breslow analysis.

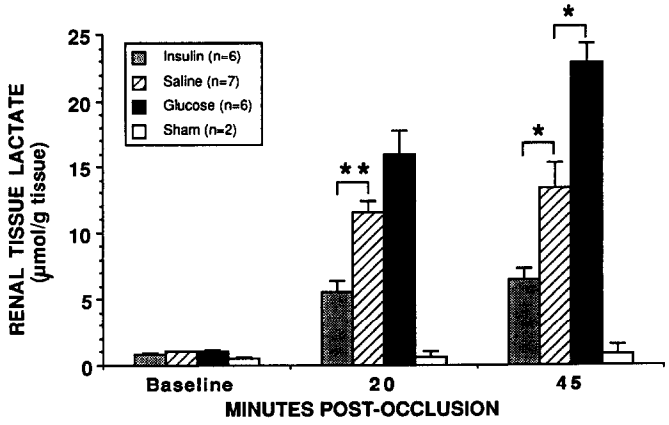

FIG. 4. Renal tissue lactate at baseline and at 20 and 45 min of ischemia in μmole/g tissue in insulin-treated (4 U/kg); saline control, glucose-treated (2 g/kg); and sham-operated, glucose-treated (2 g/kg) rats. *$P < 0.0167$, **$P < 0.001$ by Student's t test with Bonferroni correction. Sample sizes are indicated in the figure legend.

mains incomplete. Evidence in the experimental literature has identified the potential detrimental effect of glucose administration in a number of ischemia models and further evidence is provided here.

Model considerations. A 45-min ischemic period was chosen for these studies. A slightly greater increase in plasma creatinine was found in this study as compared to reports by other investigators using the same model [34, 35]. Strict maintenance of normothermia may account for the difference in postischemic renal function in our protocols.

The level of baseline functional impairment selected is important so that adverse and beneficial effects of proposed interventions can be noted. In our experiment, glucose administration did result in significant exacerbation of renal injury as compared to saline controls. In addition, despite significant elevation of plasma creatinine in the saline control group (4.7 mg/dl at 24 hr, 6.1 mg/dl at 48 hr, and 5.5 mg/dl at 72 hr), these controls were polyuric, permitting functional assessments based on urinary output and composition. (By contrast, the severe glucose-exacerbated injury was accompanied by marked oliguria.) Further, 73% of the saline control group survived the 72-hr observation period. In all but one case, this correlated with functional recovery as well. Finally, while the specific interventions in this experiment did not limit ischemic damage, significant protection has been provided using this model of renal ischemia in other work from our laboratory [36].

Intravenous glucose solutions are widely used clinically and attendant moderate hyperglycemia is common. We sought to strictly control the administered glucose load to closely parallel a clinically relevant level of hyperglycemia. In addition, isoosmotic solutions were prepared to avoid a potentially significant osmotic diuresis and the total volume was limited.

The sham-operated group provided important experimental control. It is reasonable to conclude that the anesthetic, surgical preparation, unilateral nephrectomy, and/or sampling procedures did not significantly impact on renal function in the recovery protocol.

A separate biopsy protocol was used to obtain renal tissue for lactate assay. Reproducible lactate levels required at least 50 mg of tissue. The ischemic kidney (approximately 800–900 mg in size) was biopsied twice. The remaining renal tissue showed evidence of reperfusion in all cases. The characteristics, preparation, and handling of the animals were identical between the two protocols. The plasma glucose profiles were also essentially identical permitting reasonable comparison between protocols. The sham-operated group again provided an important control. The pneumatic biopsy drill did not produce widespread renal tissue injury in that lactate levels on repeated biopsy within the same kidney did not vary from the control value among the shams.

Mechanistic considerations. Hyperglycemia-exacerbated renal ischemic damage is again demonstrated in this experiment. This concept is well established in the cerebral ischemia literature [5–28] and has been previously demonstrated by us in experimental canine renal ischemia [29]. It is important to note that the detrimental effects of hyperglycemia were apparent at far lower plasma glucose levels than previously reported [7, 8, 20, 23]. In these experiments, significant increases in postischemic renal dysfunction occurred with plasma glucose levels of only 272 ± 8 mg/dl. A possible explanation for the observed deleterious effects of glucose is the differences in baseline urine output (as a reflection of preocclusion hydration status). However, the treatment effects remain after appropriately controlling for these differences using univariate and multivariate statistical methods.

In past work, we have demonstrated that the adverse effects of hyperglycemia in an ischemic setting require continued ischemic metabolism of glucose in order to augment postischemic dysfunction. When one inhibits continued glucose metabolism in the presence of hyperglycemia, injury is not enhanced. In a model of forebrain ischemia, 2-deoxyglucose, a competitive inhibitor of the cellular glucose uptake and an inhibitor of glycolytic flux (hexokinase), provided marked reduction of postischemic neurologic deficit in the face of elevated plasma glucose levels [37].

Much of the work on the role of lactate accumulation in ischemic injury has been performed in models of myocardial and cerebral ischemia. Numerous studies, including work from our own laboratory, have established that hyperglycemia in the setting of cerebral ischemia produces functional and morphologic exacerbation of neurologic deficit [5–7, 13, 18]. Such deficits have often been associated with lactate accumulation [8, 14, 25–27]. Previously, insulin administration (with presumed reduction of lactate) has been found to be protective in models of cerebral and spinal cord ischemia [38, 39]. Neely and Grotyohann also suggest a major role for glycolytic products in myocardial ischemia [40]. Accumulation of tissue lactate during ischemia in the isolated perfused heart consistently produced a strong inverse correlation with postischemic recovery of ventricular function—an effect largely independent of tissue adenine nucleotide levels. Interestingly, in Neely's studies infusion of lactate during the reperfusion period was not detrimental, suggesting that any predominant harmful effect of lactate was during the ischemic interval. Equally compelling is recent evidence suggesting a diminished role for lactate in cerebral ischemic pathophysiology. Cerebral lactate accumulation was measured in dogs subjected to cardiac arrest following selective brain cooling and in normothermic controls [41]. Cerebral hypothermia provided significant reduction of postischemic neurologic dysfunction and mortality but *no* differences in cerebral cortical lactate accumulation were detected between brain-cooled and control dogs. There are a paucity of reports regarding the role of lactate in renal ischemia. Vogt and Farber, however, found no differences in postischemic renal histopathology in rats with tissue lactate reduction following 2-deoxyglucose pretreatment as compared to controls [42]. The initial

injury, however, was mild and baseline lactate accumulation low. No functional assessments were obtained.

In the present study, marked lactate accumulation in glucose-treated animals was associated with significant exacerbation of postischemic renal dysfunction. However, insulin-induced reduction of plasma glucose which caused significant reduction of tissue lactate failed to ameliorate postischemic injury. The reduction of tissue lactate was to levels generally felt to be innocuous to tissues. Thus, data from this study do not fully support the hypothesis that increased levels of lactate lead to exacerbation of renal ischemic damage.

An alternative explanation of the data has been suggested in the cerebral ischemia literature. Myers and others have shown that a threshold for cerebral necrosis exists at tissue lactate levels of 16–20 μmole/g tissue [16, 43]. Such a "threshold effect" for lactate could explain these data. A further postulate may be that increasing tissue lactate concentration may contribute to exacerbation of injury by further decreasing tissue pH. Thus, while the data verifying hyperglycemia-exacerbated renal ischemic damage are compelling, it remains unproved whether lactate accumulation is the mechanistic link between observed hyperglycemia and postischemic renal dysfunction. The data further suggest that lactate alone is not the predominant effector of ischemic injury in conditions of euglycemia and mild hypoglycemia.

In summary, hyperglycemia-exacerbated postischemic renal dysfunction is demonstrated. Insulin-induced reduction of plasma glucose failed to protect in this model. Finally, while insulin-induced reduction of tissue lactate did not reduce postischemic renal dysfunction, marked lactate accumulation may contribute to the marked exacerbation of dysfunction following exogenous glucose administration.

Clinical applications. Surgeons commonly deal with several settings in which renal ischemia is a predictable consequence of the operative procedure, e.g., suprarenal aortic clamp and renal transplantation. In other settings, such as "routine" aortic surgery or resuscitation from shock and trauma, renal ischemic considerations are less obvious but equally important. Optimal support of ischemic tissues has not been fully defined. Of clear importance is the need for an ongoing energy supply to continue essential cellular processes, yet continued glucose metabolism during ischemia seems to clearly be detrimental. The precise role of metabolic factors in renal ischemia are of critical importance to the understanding of organ injury. Delineation may provide potential loci for effectively altering metabolism to achieve protection from irreversible injury.

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