Opposite Effects of Diabetes on Nephrotoxic and Ischemic Acute Tubular Necrosis (43117)

HANNA WALD, HASSIDA MARKOWITZ, SHOSHANNA ZEVIN, AND MORDECAI M. POPOVTZER
Nephrology and Hypertension Services, Hadassah University Hospital, Jerusalem, Israel

Abstract. **The effect of streptozotocin-induced diabetes mellitus on two different models of acute tubular necrosis (ATN), was studied: (i) the nephrotoxic model of $HgCl_2$-induced ATN and (ii) the ischemic model of renal artery clamping for 60 min. Induction of ATN with $HgCl_2$ in normal rats decreased CrCl from 0.67 ± 0.05 to 0.1 ± 0.019 ml/min ($P < 0.001$) after 24 hr, and it deteriorated further to 0.03 ± 0.013 ml/min after 48 hr; whereas, in the diabetic rats, $HgCl_2$ decreased CrCl from 0.98 ± 0.11 only to 0.31 ± 0.037 ml/min ($P < 0.0001$), but CrCl recovered to 0.50 ± 0.08 ml/min after 48 hr.**

Bilateral clamping of renal arteries for 60 min in control and diabetic rats extremely decreased CrCl in both groups. Twenty-four hours after clamping, two of nine rats from the diabetic group died, whereas none from the control group died. Forty-eight hours after clamping, all nine rats from the diabetic group died, whereas only two rats from the control group died, and in the four surviving rats CrCl recovered slightly. Our study shows that streptozotocin-induced diabetes could not confer a general protection against ATN. It was protective against a nephrotoxic insult but aggravated the ischemic insult. An attempt to reconcile these discrepant effects is made in the Discussion.

[P.S.E.B.M. 1990, Vol 195]

Streptozotocin (STZ)-induced diabetes mellitus has been shown to protect rats against gentamicin-induced acute tubular necrosis (ATN) (1, 2). Previous studies from our laboratory (3, 4) and also from others (5, 6) have demonstrated marked increases in Na-K-ATPase in STZ-induced diabetes along most of the nephron. It should be noted in this regard that other states, such as treatment with thyroxin, salt loading, and unilateral nephrectomy (7, 8), in which increased Na-K-ATPase activity was measured also were shown to protect against various forms of ATN (9–11). On the other hand, different models of ATN have been shown to be associated with decreased Na-K-ATPase activity (12–15). Cronin *et al.* (12) and Hori *et al.* (13) have shown decreased cortical Na-K-ATPase activity in the gentamicin and uranyl nitrate models of ATN, respectively. Pfaller *et al.* (14) have demonstrated marked decrease in whole kidney Na-K-ATPase activity 24 hr after the induction of ATN by $HgCl_2$, whereas only a mild reduction in the enzymatic activity was observed after acute ischemia caused by clamping of the renal artery for 45 min. Westenfelder *et al.* (15) demonstrated decreased Na-K-ATPase activity both in the cortex and in the medulla 24 hr after the induction of ATN by glycerol.

The interrelationship between the states of increased Na-K-ATPase activity and protection against ATN which is frequently associated with decreased enzyme activity has not been defined in detail. Therefore, this study was undertaken to compare the effect of STZ-induced diabetes in which marked increases in renal Na-K-ATPase were shown on two different models of ATN (3–6): first, the nephrotoxic model of $HgCl_2$-induced ATN, and second, the ischemic model of renal artery clamping for 60 min.

Received September 8, 1989. [P.S.E.B.M. 1990, Vol 195]
Accepted April 25, 1990.

0037-9727/90/1951-0050$2.00/0

Materials and Methods

Studies were performed in male rats of the Hebrew University strain weighing 200–250 g.

Animals were placed in individual metabolic cages with free access to food and water 6–7 days before initiation of the experiment.

On the first day of study streptozotocin (Sigma, St. Louis, MO) was injected subcutaneously (5.5 mg/100

g in 0.2 ml of 0.01 *M* citrate buffer (pH 4.5), whereas control rats received 0.2 ml/100 g citrate buffer. The development of diabetes was evaluated by measuring urinary glucose with a glucotest strip. Six days after the induction of diabetes, a 24-hr urine collection was performed, and blood was drawn from the tail vein for basal renal function and blood glucose determinations. On the seventh day after the induction of diabetes, two types of ATN were induced in each group: (i) Nephrotoxic ATN (Experiment 1) was induced by injection of 0.5 mg/100 g $HgCl_2$ in 0.25 ml of saline intramuscularly, whereas a control group received 0.25 ml/100 g saline. (ii) Ischemic ATN (Experiment 2) was induced by bilateral occlusion of renal arteries for 60 min under pentobarbitol anesthesia; in the control group a sham operation was performed.

Twenty-four and 48 hr after the induction of ATN, 24-hr urine collections were performed, and blood was drawn for renal function determinations.

In Experiments 1 and 2 the following subgroups were studied: Experiment 1, Subgroup 1, normal control; Subgroup 2, normal rats receiving $HgCl_2$; Subgroup 3, diabetic rats; Subgroup 4, diabetic rats receiving $HgCl_2$. Subgroups 1 and 3 received the vehicle of $HgCl_2$. Experiment 2, Subgroup 5, normal controls; Subgroup 6, normal rats undergoing bilateral renal arteries occlusion; Subgroup 7, diabetic rats; Subgroup 8, diabetic rats undergoing bilateral renal arteries occlusion. Subgroups 5 and 7 underwent sham operations.

Three additional experiments were performed as completion to Experiments 1 and 2.

In Experiment 3, nephrotoxic ATN was induced also in a group of rats in which water diuresis was induced by adding 7.5% glucose to their drinking water for 7 days before and during the induction of ATN by $HgCl_2$.

In Experiment 4 during the 60 min of bilateral renal arteries occlusion, the rats were infused through the femoral vein with 1.5 ml/100 g/hr of 0.5% saline until recovery from the anesthesia to prevent dehydration.

In Experiment 5 in a separate experiment diabetic rats were injected with increasing doses of $HgCl_2$ to cause increasing degrees of ATN. The doses injected were 0.5, 1.0, and 2.0 mg/100 g. In this experiment a control group received only the lowest dose of $HgCl_2$, i.e., 0.5 mg/100 g, because in previous experiments it was shown that this dose caused severe ATN.

Creatinine concentration was measured by an automated picric acid method using the Gilford 3500 system. Sodium and potassium concentrations were measured using flame photometer IL 343. CrCl and Fe_{Na} were calculated.

Data are presented as mean ± SE; results were compared by a nonpaired Student's *t* test.

Results

The results of Experiment 1 are summarized in Table I. Diabetes per se was characterized by increased urine flow rate and increased water intake accompanied by increased CrCl. Blood glucose increased in the diabetic rats to 30.3 ± 1.2 mmol/liter compared with 9.5 ± 0.4 mmol/liter in controls ($P < 0.001$). Induction of ATN with $HgCl_2$ in normal rats decreased CrCl to 0.1 ± 0.019 ml/min ($P < 0.001$ compared with basal value) after 24 hr, which further deteriorated to 0.03 ± 0.013 ml/min after 48 hr. Whereas in the diabetic rats $HgCl_2$ administration decreased CrCl after 24 hr only to 0.31 ± 0.037 ml/min ($P < 0.001$ compared with $HgCl_2$ alone), which recovered to 0.50 ± 0.08 ml/min after 48 hr. Induction of ATN in intact rats was accompanied by poliuria compared with the basal state after 24 hr ($P < 0.05$) which tended to recover toward the basal state after 48 hr. Conversely, administration of $HgCl_2$ to diabetic rats was accompanied by decreased diuresis compared to the basal state after 24 hr ($P < 0.05$) which returned toward the basal level after 48 hr.

Fe_{Na} increased significantly 24 hr after the administration of $HgCl_2$ to intact rats ($P < 0.01$ compared with the basal state), and it further increased after 48 hr. In the diabetic rats, administration of $HgCl_2$ did not change Fe_{Na} after 24 hr and moderately increased Fe_{Na} after 48 hr, but this increase did not reach statistical significance.

In rats undergoing water diuresis with 7.5% glucose in the drinking water (Experiment 3), urine output averaged 135 ± 6.0 ml/24 hr. Induction of ATN in these rats by $HgCl_2$ brought about a greater decrease in CrCl after 24 hr to 0.045 ± 0.004 compared with intact rats treated with $HgCl_2$ ($P < 0.025$).

When increasing doses of $HgCl_2$ were injected to diabetic rats, after 24 hr an inverse correlation was observed between the dose of $HgCl_2$ and CrCl ($R = -0.920$, $P < 0.01$). After 48 hr, rats that received 0.5 mg/100 g $HgCl_2$ tended to recover while those receiving higher doses of $HgCl_2$ tended to deteriorate in their kidney function further. In fact CrCl in diabetic rats receiving 2.0 mg/100 mg $HgCl_2$ was similar to that of control rats receiving 0.5 mg/100 g $HgCl_2$.

The results of Experiment 2 are summarized in Table II. Diabetes per se brought about changes similar to those observed in Experiment 1. Bilateral clamping of renal arteries extremely decreased CrCl in both intact and diabetic rats after 24 hr and was accompanied by oliguria. The decrease in CrCl in the diabetic group was even greater than in the intact group, but the difference did not reach statistical significance. Twenty-four hours after clamping, two of nine rats from the diabetic group died whereas none from the intact group died. Forty-eight hours after clamping, all nine rats from the diabetic group died, whereas only two from the intact

Table I. Effect of $HgCl_2$-Induced ATN on Water Intake, Diuresis, CrCl, and $FeNa^+$ in Control and Diabetic Rats

	Control	$HgCl_2$	Diabetic	Diabetic + $HgCl_2$
Water intake (ml/24 hr)				
Basal	33.4 ± 4.7 ($n = 7$)	28.5 ± 2.8 ($n = 7$)	97.8 ± 11.3 ($n = 8$)	91.6 ± 16.4 ($n = 7$)
24-hr post-$HgCl_2$	33.7 ± 2.7 ($n = 7$)	43.3 ± 6.6 ($n = 7$)	106.0 ± 12.3 ($n = 8$)	69.9 ± 14.2 ($n = 7$)
48-hr post-$HgCl_2$	32.7 ± 6.6 ($n = 7$)	25.9 ± 4.9 ($n = 7$)	106.3 ± 15.7 ($n = 8$)	83.3 ± 19.0 ($n = 7$)
Diuresis (ml/24 hr)				
Basal	13.1 ± 2.3 ($n = 7$)	10.6 ± 1.5 ($n = 7$)	74.0 ± 9.3 ($n = 8$)	76.7 ± 13.7 ($n = 7$)
24-hr post-$HgCl_2$	12.6 ± 1.6 ($n = 7$)	20.7 ± 4.5 ($n = 7$)	78.1 ± 9.3 ($n = 8$)	45.0 ± 8.2 ($n = 7$)
48-hr post-$HgCl_2$	12.3 ± 2.2 ($n = 7$)	15.7 ± 5.9 ($n = 7$)	84.1 ± 10.6 ($n = 8$)	73.9 ± 13.3 ($n = 7$)
CrCl (ml/min)				
Basal	0.75 ± 0.025 ($n = 7$)	0.67 ± 0.051 ($n = 7$)	0.94 ± 0.09 ($n = 8$)	0.98 ± 0.11 ($n = 7$)
24-hr post-$HgCl_2$	0.74 ± 0.074 ($n = 7$)	0.10 ± 0.019 ($n = 7$)	1.03 ± 0.09 ($n = 8$)	0.31 ± 0.037 ($n = 7$)
48-hr post-$HgCl_2$	0.84 ± 0.055 ($n = 7$)	0.03 ± 0.013 ($n = 7$)	0.94 ± 0.062 ($n = 8$)	0.50 ± 0.084 ($n = 7$)
$FeNa^+$ (%)				
Basal	0.65 ± 0.10 ($n = 7$)	0.53 ± 0.023 ($n = 6$)	0.75 ± 0.12 ($n = 7$)	0.74 ± 0.05 ($n = 6$)
24-hr post-$HgCl_2$	0.60 ± 0.090 ($n = 7$)	2.52 ± 0.58 ($n = 6$)	0.86 ± 0.15 ($n = 7$)	0.57 ± 0.046 ($n = 6$)
48-hr post-$HgCl_2$	0.55 ± 0.11 ($n = 7$)	20.6 ± 3.1 ($n = 4$)	0.85 ± 0.14 ($n = 7$)	1.76 ± 0.62 ($n = 5$)

group died, and in the four surviving rats CrCl recovered slightly and was accompanied by increased diuresis. Fe_{Na} increased in both diabetic and intact groups after bilateral clamping. The increase in Fe_{Na} was more pronounced in the diabetic group, but the difference did not reach statistical significance.

Plasma K^+ concentration in the diabetic rats subjected to ischemic injury was 7.8 ± 0.9 ($n = 7$) after 24 hr, whereas in the control rats with ischemic injury it was 6.8 ± 1.0 ($n = 6$), not significant. After 48 hr, as already mentioned, all rats from the diabetic group died, whereas in the 4 surviving control rats with ischemic injury plasma K^+ was 5.6 ± 1.0 ($n = 4$).

To rule out the possibility that dehydration in the diabetic group was the cause for their increased vulnerability to the ischemic insult, we studied a group of intact and diabetic rats undergoing saline infusion during the bilateral renal arteries clamping period. The results of CrCl in this experiment (Experiment 4) are summarized in Table III. Twenty-four hours after renal arteries clamping with saline infusion, CrCl markedly decreased in both intact and diabetic rats. The decrease in CrCl, however, was significantly greater in the diabetic group ($P < 0.05$). After 48 hr of clamping, five of five from the diabetic rats died, whereas only one of five rats from the intact group died. CrCl of the four surviving rats improved after 48 hr.

Discussion

The results of this study show that streptozotocin-induced diabetes mellitus affects the development of nephrotoxic and ischemic ATN in opposite ways. Diabetes protects against nephrotoxic ATN, whereas it aggravates the ischemic form of ATN. The reasons for this discrepancy are not readily understood. Protection by diabetes against a variety of nephrotoxic forms of ATN were studied (1, 2, 16, 17), whereas the effect of diabetes on ischemic ATN had not been examined previously. In all cases of nephrotoxic ATN, i.e., gentamicin, cis-platinum, uranyl nitrate, diabetes exhibited a protective effect (1, 2, 16, 17). In this study we demonstrate the same protection by diabetes against $HgCl_2$-induced ATN.

Our original hypothesis was that the common denominator for the protection conferred by streptozotocin-induced diabetes against a variety of nephrotoxic insults (1, 2, 16, 17) was the increase in renal Na-K-ATPase (3–6). Increase in this enzymatic activity was thought to protect against ATN by conserving the integrity of cellular volume and ion composition (12), similar to the protection against ATN in other states of increased Na-K-ATPase, as during administration of thyroxine (9). This hypothesis became questionable when we realized that diabetes was not protective

Table II. Effect of Bilateral Clamping of Renal Arteries for 60 Min on Water Intake, Diuresis, CrCl, and $FeNa^+$ in Control and Diabetic Rats

	Control	Clamping 60 min	Diabetic	Diabetic ± clamping 60 min
Water intake (ml/24 hr)				
Basal	33.7 ± 7 ($n = 8$)	36.4 ± 8.3 ($n = 6$)	95.8 ± 14.1 ($n = 8$)	89.3 ± 14.8 ($n = 9$)
24-hr postclamping	39.3 ± 13.9 ($n = 8$)	21.6 ± 8.3 ($n = 6$)	82.7 ± 20.1 ($n = 8$)	20 ± 6 ($n = 7$)[a]
48-hr postclamping	32.8 ± 9.2 ($n = 8$)	31.6 ± 10 ($n = 4$)[a]	88.1 ± 26 ($n = 8$)	—[b]
Diuresis (ml/24 hr)				
Basal	12.5 ± 7.1 ($n = 8$)	13.2 ± 8.3 ($n = 6$)	68.5 ± 12 ($n = 8$)	65.4 ± 10.3 ($n = 9$)
24-hr postclamping	16.7 ± 6.3 ($n = 8$)	7.8 ± 5.7 ($n = 6$)	50.4 ± 6.6 ($n = 8$)	7.6 ± 4.7 ($n = 7$)[a]
48-hr postclamping	14.5 ± 5.2 ($n = 8$)	21.3 ± 16.5 ($n = 4$)[a]	56.4 ± 12.1 ($n = 8$)	—[b]
CrCl (ml/min)				
Basal clamping	0.74 ± 0.13 ($n = 8$)	0.72 ± 0.11 ($n = 6$)	1.03 ± 0.16 ($n = 8$)	0.98 ± 0.12 ($n = 9$)
24-hr postclamping	0.56 ± 0.12 ($n = 8$)	0.06 ± 0.03 ($n = 6$)	0.89 ± 0.16 ($n = 8$)	0.012 ± 0.008 ($n = 7$)[a]
48-hr postclamping	0.70 ± 0.11 ($n = 8$)	0.17 ± 0.08 ($n = 4$)[a]	0.93 ± 0.20 ($n = 8$)	—[b]
$FeNa^+$ (%)				
Basal	0.46 ± 0.19 ($n = 8$)	0.57 ± 0.17 ($n = 6$)	1.03 ± 0.4 ($n = 8$)	0.95 ± 0.3 ($n = 9$)
24-hr postclamping	0.69 ± 0.15 ($n = 8$)	3.5 ± 2.7 ($n = 6$)	0.67 ± 0.15 ($n = 8$)	20.6 ± 18.3 ($n = 7$)[a]
48-hr postclamping	0.49 ± 0.11 ($n = 8$)	3.8 ± 2.7 ($n = 4$)[a]	0.54 ± 0.14 ($n = 8$)	—[b]

[a] Two dead.
[b] Nine dead.

Table III. Effect of Bilateral Clamping of Renal Arteries on CrCl in Control and Diabetic Rats Undergoing 0.5% Saline Infusion

	Control	Clamping 60 min	Diabetic	Diabetic ± clamping 60 min
Basal	0.75 ± 0.09 ($n = 5$)	0.70 ± 0.19 ($n = 5$)	1.16 ± 0.15 ($n = 5$)	1.05 ± 0.16 ($n = 5$)
24-hr postclamping	0.62 ± 0.3 ($n = 5$)	0.04 ± 0.01 ($n = 5$)	0.93 ± 0.11 ($n = 5$)	0.016 ± 0.001 ($n = 5$)
48-hr postclamping	0.64 ± 0.19 ($n = 5$)	0.19 ± 0.11 ($n = 4$)[a]	0.98 ± 0.22 ($n = 5$)	—[b]

[a] One dead.
[b] Five dead.

against the ischemic insult. Furthermore, diabetes aggravated the ischemic form of ATN.

A possibility to reconcile the discrepant effects of diabetes on nephrotoxic and ischemic ATN may be found in part in the study of Ramsammy *et al.* (18). Similar to Teixeira *et al.* (1), these authors have shown that diabetes decreased the uptake of gentamicin into the renal tissue. But, once the doses of gentamicin were increased and the concentration within the kidney reached a critical threshold, the rats developed a pattern of toxic injury indistinguishable from that of nondiabetic rats. Presumably, a similar mechanism also underlied the protection by diabetes against other nephrotoxic agents including $HgCl_2$. To test this possibility, we injected diabetic rats with increasing doses of $HgCl_2$ (Table IV). An inverse correlation was observed between the dose of $HgCl_2$ and CrCl. In fact, 20 mg/kg $HgCl_2$ induced an injury in diabetic rats similar to that

Table IV. Effect of Increasing Doses of $HgCl_2$ on CrCl in Diabetic Rats

	Control + $HgCl_2$ (0.5 mg/100 g)	Diabetic + $HgCl_2$ (0.5 mg/100 g)	Diabetic + $HgCl_2$ (1.0 mg/100 g)	Diabetic + $HgCl_2$ (2.0 mg/100 g)
Basal	0.8 ± 0.04 (n = 9)	—	1.19 ± 0.09 (n = 17)	—
24-hr post-$HgCl_2$	0.11 ± 0.02 (n = 9)	0.5 ± 0.05 (n = 6)	0.27 ± 0.07 (n = 5)	0.12 ± 0.04 (n = 6)
48-hr post-$HgCl_2$	0.015 ± 0.008 (n = 9)	0.63 ± 0.13 (n = 5)	0.14 ± 0.07 (n = 4)	0.08 ± 0.06 (n = 5)

caused by 5 mg/kg in intact rats. These results support the assumption that diabetes may decrease the uptake of $HgCl_2$ into the renal tissue. However, induction of water diuresis in rats by letting them drink 7.5% glucose in water did not protect them against the nephrotoxic insult of $HgCl_2$, similar to what was shown by Teixeina *et al.* (1) in rats with diabetes insipidus. The aggravation of ischemic ATN by diabetes may be related to the concept of cellular hypoxia of the renal medulla (19, 20) increasing the vulnerability of the renal medulla to anoxic ischemic injury due to limited oxygen supply to this segment even under normal conditions (21). Thus, in diabetes when the pump activity along most of the nephron was enhanced markedly (3–6) and consequently the energy demand of the pump was largely increased, greater vulnerability toward an ischemic insult might be expected.

In a recent study from our laboratory we demonstrated clearly that glycerol-induced ATN, which represents an ischemic insult to the kidney (22), was associated with a marked decrease in Na-K-ATPase activity mainly in the medullary thick ascending limb of Henle's loop (MTAL) even in its moderate form (23), indicating the high vulnerability of this nephron site to ischemic injury. Because the cells of the MTAL normally might operate on the verge of anoxia (20) and the increased Na-K-ATPase activity in the MTAL in diabetes (3, 4) might increase the energy demand of these cells, the increased vulnerability of kidneys of diabetic rats to ischemia might be well understood.

To rule out the possibility that volume depletion in the diabetic group was the cause for the aggravation of the ischemic ATN, we also studied a group of rats undergoing saline infusions during the period of occlusion of the renal arteries. In spite of saline infusion diabetic rats undergoing bilateral occlusion were more vulnerable to the ischemic insult compared to nondiabetic rats.

Our study shows that streptocotozin-induced diabetes could not confer a general protection against ATN. It was protective against a nephrotoxic insult but aggravated the ischemic insult.

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