Effects of Streptozotocin-Induced Diabetes and Insulin Treatment on Blood Pressure in the Male Rat (43860)

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Abstract. **Hyperinsulinemia may link diabetes to hypertension. We evaluated the effects of insulin on blood glucose and blood pressure in control and streptozotocin (STZ)-induced (60 mg/kg, iv) diabetes. Insulin was given daily for 10–14 weeks to both diabetic (0, 1, 2, and 3 U) and control (0, 2, and 3 U) male rats (n = 7–8/group). Indirect and direct blood pressures were measured as were blood glucose and several metabolic parameters. All treated rats became hyperinsulinemic. Untreated and 1 U insulin-treated diabetic rats were hyperglycemic. Higher doses of insulin significantly reduced blood glucoses in diabetic animals. Indirect blood pressure measurements were unchanged between groups. However, when measured directly, the untreated diabetic rats had significantly lower pressures that did untreated controls. Insulin treatment at dosages above 1 U normalized blood pressure in diabetic animals. These same doses of insulin also restored to normal all the metabolic parameters associated with diabetes. Insulin treatment did not affect any of the parameters evaluated in nondiabetic rats. Collectively, the results show that STZ-induced diabetes results in a decrease in blood pressure and that insulin treatment can restore blood pressure in diabetic rats. Although the results suggest that insulin may be involved in restoring blood pressure in animals with a carbohydrate imbalance, the precise mechanism for elevating blood pressure is not known with certainty.** [P.S.E.B.M. 1995, Vol 208]

Epidemiological evidence suggests that there is a close association between diabetes and hypertension. A possible common denominator between these two diseases is the state of insulin resistance and/or hyperinsulinemia. Diabetes is associated with hyperinsulinemia and/or a state of insulin resistance (1, 2). Plasma insulin levels also are elevated in patients with essential hypertension (3–5). Animal studies demonstrate a similar relationship between insulin and hypertension (6, 7). Numerous investigators have shown that diabetic animals are hypertensive (8–10). Inducement of a hyperinsulinemic state in animals has been associated with hypertension as well (6, 7, 11). Insulin and/or insulin resistance is involved with numerous aspects of physiology which are important in blood pressure control mechanisms. Insulin has been shown to affect renal sodium handling, vasopressor activity, the sympathetic nervous system, the renin angiotensin system, intracellular calcium metabolism, and proliferation of vascular smooth muscle (2, 12, 13). Each and all of these effects can be associated with an increase in blood pressure.

It has been reported by several investigators (8–10) that streptozotocin (STZ) administration in rats resulted in the development of diabetes and a subsequent hypertension in these animals. However the literature on this topic remains controversial, with several reports which do not support this finding (14–16). Some of the reasons underlying the divergent findings between studies may include differences in sex, strain, duration of the diabetes, and the dose and modes of induction of the STZ. Moreover, the method by which one measures blood pressure may have a

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Received June 7, 1994. [P.S.E.B.M. 1995, Vol 208]
Accepted September 28, 1994.

0037-9727/95/2083-0300$10.50/0

major effect on the results obtained. For example, Kusaka *et al.* (15) recently reported that STZ-induced diabetes in the Wistar-Kyoto (WKY) rat resulted in an increase in blood pressure when measured indirectly, however, direct blood pressure measurements revealed a decrease in blood pressure. Similarly, direct measurements of blood pressure have demonstrated that STZ-treated rats have lower systolic blood pressure than their corresponding controls (16). Cardiovascular complications associated with diabetes thus may influence the indirect blood pressure recordings.

The purpose of the present study was to determine if blood pressure is altered in the STZ-induced diabetic rat. Both indirect and direct blood pressures were measured in Sprague-Dawley rats. Additionally, since insulin has been implicated in various aspects of blood pressure regulation, we hypothesized that graded doses of exogenous insulin would increase blood pressure in both control and diabetic animals. This study addressed this hypothesis.

Materials and Methods

Fifty-six male Sprague-Dawley rats, initially weighing 200–225 g, were purchased from Charles Rivers (Wilmington, DE). The animals were housed in hanging stainless steel cages in a room maintained at 24° ± 1°C with a 14:10-hr light:dark cycle (lights on from 5:00 AM to 7:00 PM). Animals had access to a standard rat chow (Purina Rat Chow, St. Louis, MO) and tap water *ad libitum*. Animals were randomly divided into two groups. Following an overnight fast, 32 animals were lightly anesthetized with methoxyflurane (Metofane; Pitman-Moore, Inc., Mundelein, IL) and administered streptozotocin (STZ) (Sigma Chemical Co., St. Louis, MO) via the jugular vein at a dose of 60 mg/kg. Control animals (n = 24) were administered the vehicle, a citrate buffer (0.1 *M* citric acid and 0.1 *M* sodium citrate, pH 4.5). Three days later blood glucose was determined utilizing a YSI Sport glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, OH). Whole blood samples were collected from the tip of the rat tail in unanesthetized rats. At this time, animals were further divided into additional groups. Eight rats in the control group were administered 2 U of insulin (Protamine Zinc & Iletin® II; Eli Lilly and Co., Indianapolis, IN), eight were administered 3 U of insulin, and eight served as untreated controls. The 32 STZ-treated animals were equally divided into untreated, 1 U, 2 U, and 3 U insulin treatment groups. Insulin was administered sc between 4:00 and 5:00 PM daily.

Indirect blood pressures were obtained weekly via a standard tail cuff technique utilizing a Narco Biosystems pneumatic pulse transducer and a Model DBM 4B physiograph recorder (Narco Bio-systems, Houston, TX). Animals were warmed for 5 min prior to the evaluation of indirect blood pressure. Blood pressures were measured in the afternoons. Weekly blood glucose was obtained from the rat tail between 1:00 and 3:00 PM except for the fifth and sixth blood samples which were obtained later in the day (3:00 to 5:00 PM). Blood glucose was determined using a YSI Sport glucose analyzer. During the 5th week of treatment, four untreated control animals, five controls + 2 U insulin, five untreated STZ animals, five 2 U insulin-treated and five 3 U insulin-treated STZ animals were placed in metabolic cages. Daily water intake, food intake, and urinary volume were measured between 10:00 AM and 12:00 noon. Urine samples were then measured daily for urinary glucose by utilizing a YSI, Model 27 glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, OH) and urinary sodium and potassium using an ion-sensitive electrode method (NOVA Biomedical, Newton, MA).

During the 10th through the 14th week of the study, two to four animals per day were randomly chosen and prepared for direct measurement of blood pressure. Each animal was anesthetized with a ketamine (30 mg/kg), xylazine HCl (6 mg/kg), and acepromazine (1 mg/kg) rodent anesthesia cocktail mixture (0.7 ml/kg, im) and the left carotid artery cannulated with PE 50 tubing. The cannula was subcutaneously threaded around the neck and exteriorized dorsally between the shoulders. The cannula was filled with a heparin solution (10 U/ml) and sealed with a solid 22-gauge stylet. Twenty four hours later, direct blood pressure of each rat was monitored with a pressure transducer (Model P-1000; Narco-Biosystems), and the data was recorded on a four-channel physiograph (Mark IV; Narco-Biosystems). After the catheter was connected to the transducer a 1-hr equilibration period was utilized before blood pressures were recorded between 9:00 and 10:00 AM. During the measurement period, each animal was unanesthetized and free-moving in its home cage as previously described (17). Animals were sacrificed the following morning and nonfasted trunk blood collected between 8:00 and 9:00 AM for determination of blood glucose and glycated hemoglobin (Hb). Presence of cataract formation was observed and recorded at the time of sacrifice. Glycated Hb was determined utilizing a Glyc-affin GHB kit from Isolab Inc. (Akron, OH). Serum sodium and potassium were assessed with the ion-sensitive electrode method (NOVA sodium/potassium analyzer). The serum was also stored at 4°C for subsequent determination of insulin. Insulin concentrations were assayed by RIA utilizing a coat-a-count kit (Diagnostic Products Corp., Los Angeles, CA).

All parameters investigated were compared by a one-way ANOVA followed by a Fisher's LSD post hoc test. Repeated analysis of variance was used when comparing parameters over time. All analysis was de-

termined using a SuperAnova® statistical program and a Macintosh computer. Significance level was set at $p < 0.05$. All data are expressed as the mean ± 1 SEM.

Results

Prior to any treatment, all groups had similar body weights. The effect of both STZ and insulin treatment on body weight gain are summarized in Figure 1. Repeated analysis of variance revealed a significant effect of time, treatment, and an interaction. The growth pattern of the untreated STZ rat displayed a marked decrease compared with all other groups. Body weights in this untreated diabetic group stabilized at about 300 g by the 5th week of therapy. The 1 U insulin-treated STZ group displayed a growth pattern that was intermediate between the untreated STZ and all other groups. This group was significantly higher than the untreated diabetics but significantly lower than all other groups. Although the other insulin-treated groups appeared to gain more weight near the end of the therapy regimen, no significant differences were observed when compared with the control group.

Weekly blood glucose determinations are summarized in Figure 2. Three days after administration of STZ and prior to administration of insulin, all four STZ-treated groups displayed a similar hyperglycemia of about 300 mg/dl. Insulin treatment at the 2- and 3-U, but not the 1-U dose, significantly lowered blood glucose for the duration of the treatment regimen. The slight rise in blood glucose at treatment Day 31 and 38 was probably a result of a later time of sampling (3:00 to 5:00 PM) compared with the 1:00 to 3:00 PM sampling time on all other collection days. There were no significant effects of insulin treatment on blood glucose in the control groups. Repeated analysis of variance of the blood glucose data demonstrated a significant effect of time, treatment, and an interaction.

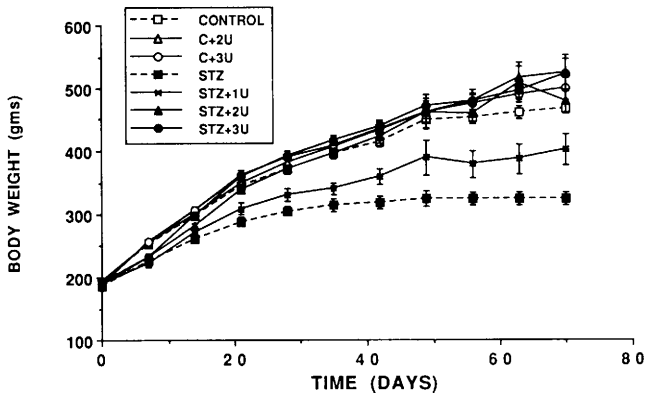

Figure 1. Effect of STZ-induced diabetes and daily insulin administration on body weight during 10 weeks of continuous treatment. STZ (60 mg/kg, iv) was administered at time zero and daily insulin treatment (0, 1, 2, or 3 U) was initiated 3 days later. Each point represents the mean ± SEM for six to eight animals per group.

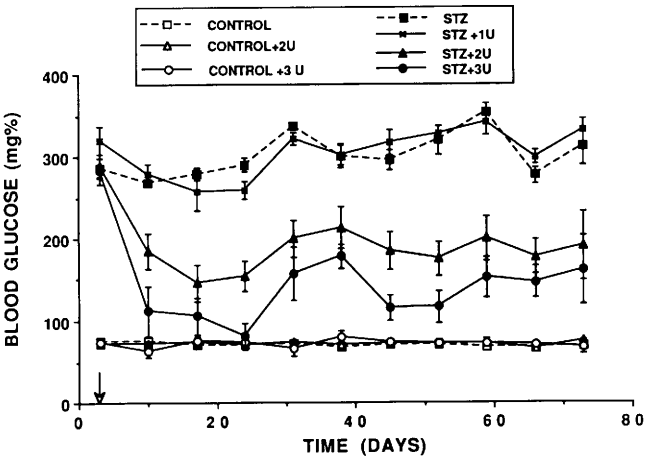

Figure 2. Effect of STZ-induced diabetes and daily insulin administration on blood glucose during 10 weeks of continuous treatment. STZ (60 mg/kg, iv) was administered at time zero and daily (5:00 PM) insulin treatment (0, 1, 2, or 3 U) was initiated 3 days later (depicted by arrow). Blood samples were obtained from the rat tail between 1:00 and 3:00 PM (except for the fifth and sixth sampling periods, which were obtained between 3:00 and 5:00 PM). Each point represents the mean ± 1 SEM for six to eight animals per group.

The metabolic parameters assessed during the 5th week of STZ treatment are summarized in Table I. Untreated diabetic rats showed the expected polydipsia, hyperphagia, polyuria, and glycosuria compared with controls. These metabolic parameters were significantly reduced in the insulin-treated diabetic animals, to values that were no longer different from controls. Likewise, urinary excretion of both sodium and potassium were elevated significantly in untreated diabetic rats and normalized in insulin-treated diabetic rats. However, no significant differences were observed in any of these parameters between control and the 2 U insulin-treated control group.

Indirect blood pressures were monitored weekly from the 2nd through the 10th week of treatment in each animal. No significant effects of either time or treatment were observed among the groups. The average mean indirect blood pressure during Week 2 through 10 of the study were 113 ± 1, 114 ± 1, 114 ± 1, 113 ± 1, 112 ± 1, 115 ± 2, 114 ± 1 mm Hg in the control, 1 U insulin-treated control, 2 U insulin-treated control, untreated diabetic, 1 U insulin-treated diabetic, 2 U insulin-treated diabetic, and 3 U insulin-treated diabetic, respectively. During the 10th through 14th week of treatment, direct blood pressures were ascertained in each of the animals. These data are summarized in Figure 3. Mean blood pressure was significantly lower in the untreated STZ diabetic group than in the untreated control group. Insulin treatment significantly elevated the blood pressures in the 2- and 3-U diabetic groups to that observed in the control groups. Similar statistical findings also were observed when the data was summarized either as mean systolic or diastolic pressure. Insulin treatment did not affect

Table I. Effect of 5 Weeks of Insulin Treatment on 24-hr Food and Water Intake, Urinary Output, Urinary Glucose, and Urinary Na^+ and K^+ Excretion in Control and Diabetic Male Rats

Experimental group	Body wt (g)	Water intake (ml/24 hr)	Food intake (g/24 hr)	Urinary volume (ml/24 hr)	Urinary glucose excretion (g/24 hr)	Urinary Na^+ excretion (mEq/24 hr)	Urinary K^+ excretion (mEq/24 hr)
Control (n = 4)	397 ± 11	40.0 ± 1.1	27.1 ± 1.1	20.5 ± 1.0	0.014 ± 0.002	2.8 ± 0.3	3.0 ± 0.3
Control + 2 U insulin (n = 5)	403 ± 11[a]	41.8 ± 1.7[a]	27.0 ± 1.4[a]	24.6 ± 1.0[a]	0.013 ± 0.002[a]	2.7 ± 0.6[a]	3.1 ± 0.3[a]
Diabetic (n = 5)	303 ± 12[b]	215.8 ± 21.8[b]	44.6 ± 3.3[b]	198.2 ± 21.0[b]	17.5 ± 1.3[b]	4.0 ± 0.4[b]	7.8 ± 0.6[b]
Diabetic + 2 U insulin (n = 5)	404 ± 7[a]	62.8 ± 4.0[a]	30.4 ± 1.2[a]	43.4 ± 1.2[a]	0.49 ± 0.11[a]	3.1 ± 0.3[a]	4.9 ± 0.7[a,b]
Diabetic + 3 U insulin (n = 5)	409 ± 10[a]	54.4 ± 1.8[a]	27.8 ± 0.4[a]	40.2 ± 4.6[a]	0.80 ± .34[a]	2.8 ± 0.4[a]	4.2 ± 0.2[a]

Note. Data expressed as mean ± 1 SEM.
[a] Different from untreated diabetic $P < 0.05$.
[b] Different from control $P < 0.05$.

blood pressure in control animals. These results thus demonstrate that STZ treatment for 10–14 weeks does not produce a hypertensive state.

Figure 4 summarizes the terminal blood glucose (Fig. 4A) and % glycated Hb (Fig. 4B) data. The results indicate that blood glucose and glycated Hb are significantly elevated in diabetic rats compared with controls. Insulin treatment did not affect either parameter in control animals. However, insulin treatment significantly reduced both blood glucose and glycated Hb in a dose-dependent-like manner in the diabetic animals. Blood glucose was significantly decreased at this sampling time for all three insulin-treated diabetic rats compared with the untreated diabetic. Blood glucose in the 3 U insulin-treated diabetic group (56 ± 9 mg%) was also significantly lower than that of the 1 U insulin-treated group (156 ± 64 mg%). The reduced blood glucose in all three insulin-treated diabetic groups was no longer significantly different from that observed in any of the control groups (70–90 mg%). In contrast to blood glucose, glycated Hb was significantly reduced from untreated diabetics (16.2% ± 1.3%) in the 2 and 3 U insulin-treated groups (7.6% ± 1.2% and 5.5% ± 0.7%, respectively), but not in the 1

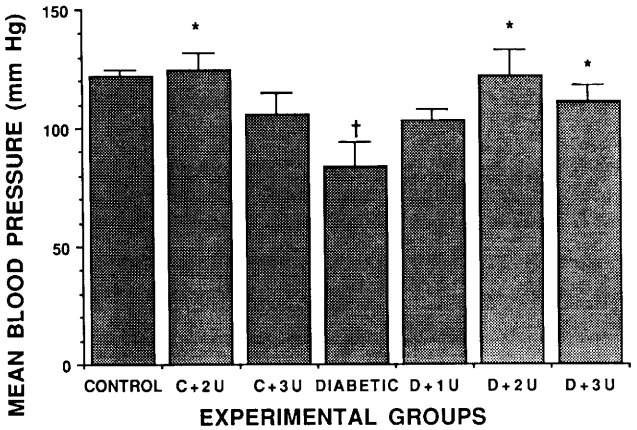

Figure 3. Effect of STZ-induced diabetes and daily insulin administration on terminal direct mean blood pressure. Animals were randomly terminated 10–14 weeks following initiation of the treatments. All samples were obtained in unanesthetized, free moving animals 24 hr after cannulation of the carotid artery. †Significant ($P < 0.05$) difference from the control group. *Significant ($P < 0.05$) difference from the untreated diabetic rat. Each point represents the mean ± 1 SEM for five to seven animals per group.

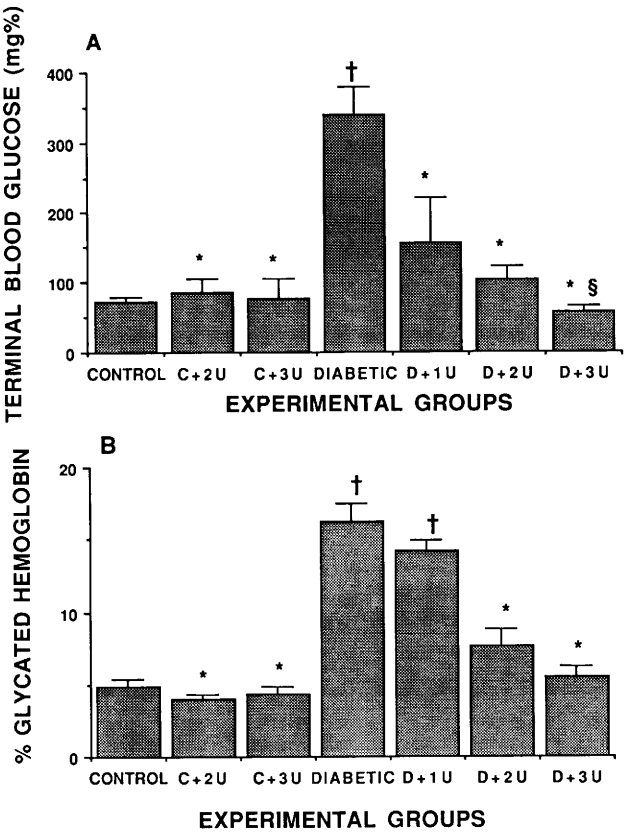

Figure 4. Effect of STZ-induced diabetes and daily insulin administration on terminal blood glucose (A) and glycated hemoglobin (B) concentrations. Animals were randomly terminated 10–14 weeks following initiation of the treatments. All samples were obtained from trunk blood between 8:00 and 9:00 AM on the day of sacrifice. †Significant ($P < 0.05$) difference from the control group. *Significant ($P < 0.05$) difference from the untreated diabetic rat. §Significant ($P < 0.05$) difference from the diabetic group treated with 1 U insulin. Each point represents the mean ± 1 SEM for five to seven animals per group.

U insulin-treated group (14.2% ± 0.7%). Values obtained in the 2 and 3 U insulin-treated diabetic groups were similar to that of the control groups (4%–5%). At the termination of the experiment each animal also was checked for the presence of cataracts. Cataracts were only observed in the untreated STZ group and the STZ + 1 U insulin group. In both of these groups an equal number of cataracts (37%) were observed.

At the time of sacrifice, serum sodium and potassium concentrations were ascertained. Neither STZ treatment nor insulin therapy significantly altered serum potassium (data not shown). However, serum sodium levels were significantly different between the untreated STZ (122.8 ± 4.3 mEq/l) and the 3 U insulin-treated, diabetic group (142.5 ± 1.7 mEq/l). Serum concentrations for the controls, 2 and 3 U insulin controls, 1 U, and 2 U insulin-treated STZ diabetic animals were 132.4 ± 6.1, 134.4 ± 8.3, 141.7 ± 4.5, 130.5 ± 4.7, and 137.7 ± 4.2 mEq/l, respectively.

At the conclusion of the study, serum insulin also was determined. Insulin treatment resulted in a significant hyperinsulinemic state in both the 2 U (754 ± 250 μU/ml) and 3 U (904 ± 242 μU/ml) insulin-treated control groups. Although insulin concentrations were almost five times lower in the untreated diabetic group (9 ± 1 μU/ml) compared with the control group (43 ± 8 μU/ml), this difference fell just out of significance. Insulin treatment in the diabetic animals also appeared to be elevated in a dose dependent manner with levels reaching 112 ± 31, 330 ± 61, and 503 ± 178 μU/ml in the 1, 2, and 3 U insulin-treated diabetic rats, respectively.

Discussion

In the current study, we investigated the development of hypertension in the STZ diabetic rat. We had hypothesized that exogenous insulin could induce a hyperinsulinemic state and increase blood pressure in these diabetic rats. Our results demonstrate that blood pressure, measured directly, was reduced rather than elevated in the STZ diabetic animal. In addition, our results suggest that an exogenously-induced hyperinsulinemic state in the diabetic, but not in the control, animal can result in an elevation in blood pressure. It has previously been reported that insulin treatment in Type I diabetics can result in a hyperinsulinemic state (1). It has also been reported that blood pressure was significantly reduced in hypertensive, but not normotensive, insulin-treated Type II diabetics when insulin doses were reduced (18). Thus, it can be inferred that by restoring insulin, blood pressures will increase in the diabetic. Our results in the insulin-treated STZ diabetic rat are consistent with the results from these human studies. However, it is important to note that this increase in blood pressure only resulted in a restoration to a normotensive state.

Although several groups have demonstrated that blood pressure is elevated in STZ diabetic rats, the majority of these reports utilize indirect, not direct, methods for the measurement of blood pressure (8–10). Our indirect pressure measurements failed to show any significant blood pressure effects among the experimental groups. However, our direct measurements revealed a significant decrease in blood pressure in the untreated diabetic animal. This latter finding is consistent with a prior study (16) and confirms that the method by which blood pressure is ascertained may explain to some degree some of the differences reported in the literature for the STZ diabetic rat. Kusaka *et al.* (15) previously demonstrated in both SHR and WKY rats that administration of STZ resulted in a reduction in blood pressure when measured directly in unrestrained animals via a cannula inserted in the aorta. In these same animals, utilizing the indirect rat tail method in unanesthetized, restrained rats, a hypertensive state was observed. The authors proposed that the differences in blood pressure with the two methods was most likely a result of the severe emaciation of the rat tail in the diabetic state and not due to heating or restraint. They theorized that STZ-diabetes resulted in structural changes in the rat tail such as a reduction of the skeletal muscular mass. If these structural changes do occur, extra pressure above the normal maximum would be required to occlude the tail artery, resulting in an apparent increase in indirect pressure and a discrepancy from direct blood pressure measurements. Our results demonstrate similar findings of Kusada *et al.* (15) albeit in a different strain of rat. Therefore, although most investigators find that indirect blood pressure measurements usually accurately reflect measurements obtained with direct measurement techniques, this relationship may not hold true in the STZ diabetic rat.

There are several possible explanations why a reduction in blood pressure would be manifest in the STZ diabetic rat. For example, this reduced blood pressure may be a result of the decrease in pressor responsiveness previously observed in the STZ diabetic animal (16, 19, 20). It is also possible that the diabetes-induced elevation in plasma glucose concentration and plasma osmolarity may cause vasodilation (21) and a resulting reduction in blood pressure. The report that blood pressure falls in the Goldblatt two kidney model of hypertension in rats made diabetic with STZ (20) also suggests that the diabetic state and/or the resulting hyperglycemia can result in a lowering of blood pressure. It is also possible that the reduced blood pressure observed in the diabetic rat could be related to alterations in the renin angiotensin system which in turn have been associated with STZ-induced diabetes. Plasma renin activity (PRA) has been shown to be reduced in STZ diabetic rats (8) as well as renal

renin concentrations (9). The increased sodium excretion in the untreated diabetic observed in the current study and in a previous study (9) is also suggestive of some abnormality in the renin angiotensin system of the STZ diabetic rat. The reduced body weight associated with diabetes could also result in a lowered blood pressure in this group. Further experiments are needed to elucidate the possible mechanism(s) for this observation of a reduced blood pressure in the STZ diabetic rat.

That insulin treatment increased blood pressure in diabetic rats to control levels without affecting the blood pressure in control animals raises some intriguing questions. There are several possible mechanisms by which the hyperinsulinemic state can increase blood pressure in the diabetic animal. One way blood pressure could be elevated in the insulin-treated diabetic rat is by altering the sympathetic nervous system. It has been reported that the sympathetic nervous system activity is reduced in STZ diabetic rats and this reduction can be prevented with insulin treatment (22). Similarly, plasma catecholamine concentrations also have been reported to increase with insulin treatment in diabetic animals (23). Hyperinsulinemic states have been associated with an enhanced sympathetic nervous system (12) which can play a role in raising blood pressure. It is also possible that blood pressure can be altered by changes in pressor responses and that insulin can produce such changes. Drury (24) demonstrated that in Type I diabetic patients without complications and on insulin therapy responded to the infusion of AII with in a greater increase in both systolic and diastolic pressures than did control patients. However, no modifications of blood pressure response to AII were observed in non diabetic patients given exogenous insulin (25). This suggests either that the vascular hyperresponsiveness to AII is not a direct result of insulin or that the effect of insulin may differ between control and diabetic individuals. It is also possible that the hyperglycemia, which occurs in the diabetic animal, may affect blood pressure control mechanisms. However, we did not find a significant correlation between blood glucose and mean blood pressure, although a trend did exist.

Another possible mechanism by which insulin may increase blood pressure is by increasing renal sodium retention. We and others (9) have demonstrated that the natriuresis observed in the untreated diabetic rat is reduced within insulin treatment. However, the antinatriuretic effect of insulin on sodium reabsorption was not apparent in insulin-treated control animals even though they too were hyperinsulinemic. These results in rats are similar to those observed in both Type I and Type II diabetic patients (18, 26). Interestingly, although the effects on urinary volume, urinary sodium and body weight were similar in a study of hypertensive and normotensive Type II diabetic patients after reduction of insulin therapy, blood pressures were significantly reduced only in the hypertensive diabetic patients (18). These findings are consistent with the suggestion of DeFronzo (27) that the effects of insulin on sodium reabsorption play an important contributory role in the hypertension observed in the obese and diabetic patient. Thus, the reduction in urinary sodium observed in the insulin-treated diabetic, but not in the insulin-treated control, may play a role in the restoration of normal blood pressure observed in these insulin-treated diabetic animals.

The lack of effect of insulin on blood pressure in control animals has been observed previously in the dog (30), despite the fact that insulin caused a transient decrease in sodium excretion and a mild sodium retention. It therefore appears that for insulin to affect blood pressure, some prior alteration in glucose metabolism and/or insulin resistance may be required. In fact, several investigators contend that the development of insulin resistance, not hyperinsulinemia per se, is the pathogenic factor in the development of hypertension (28, 29). Furthermore, it has been suggested that the effect of insulin on blood pressure also may be dependent on the concentration of sodium in the diet (31). Further studies are required to evaluate the differential effects of hyperinsulinemia and insulin resistance in control and diabetic animals.

The hyperphagia, polydipsia, polyuria, glycosuria, hyperglycemia, and elevated glycated Hb observed in the diabetic rat were all reversed with insulin treatment above 1 U. Cataract formation was only present in the untreated and 1 U insulin-treated diabetic, suggesting that higher doses of insulin were required for near normalization of numerous alterations associated with diabetes. However, as with all the other parameters assessed, insulin treatment had no effect in control animals, despite the fact that a more marked hyperinsulinemic state was observed in these insulin-treated control animals. There are at least two possibilities that may explain this finding. One is that in a normal animal, although insulin level is significantly elevated with treatment, other counterregulatory mechanisms exist to override these hyperinsulinemic effects. These counterregulatory mechanisms may be dysfunctional in the diabetic animal. It is also possible that the metabolism of insulin may be different between diabetic and control animals.

Collectively, the results demonstrate that STZ-induced diabetes does not result in hypertension. Direct blood pressure observations indicate that blood pressure is actually reduced in 10- to 14-week STZ diabetic animals. Furthermore, insulin treatment, at levels which significantly lower blood glucose and glycated Hb restore blood pressure to untreated control values in diabetic animals without affecting control an-

imals. The current data suggest that sodium retention may be a mechanism by which the hyperinsulinemic state can elevate blood pressure. However, several other mechanisms may be working either alone or in concert with one other to increase blood pressure in the diabetic rat. Although there are several reports of hyperinsulinemia resulting in an elevation in blood pressure in rats, no such alterations were observed in the hyperinsulinemic non-diabetic animal. These results therefore suggest that other conditions are required for blood pressure to rise. The results also suggest that the hyperinsulinemic state which occurs following high carbohydrate feeding (6, 7, 31) may not be the sole affector for the hypertension observed in rats and, quite recently, in dogs (32). One major factor that has been associated with insulin and hypertension is the state of insulin resistance. Whether this state exists in either the STZ rat or control rat treated with daily insulin was not determined in the current study. Further studies may be necessary to investigate the effects of hyperinsulinemia/insulin resistance on blood pressure before any definite conclusions can be ascertained.

The authors would like to thank Linda Panchou for preparation of the manuscript and Annie McGill-Weeks for technical assistance. This work was supported in part by the American Heart Association, Florida Affiliate, and National Institutes of Health Grant HD18133.

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