Renin Secretion by the Spontaneously Diabetic Rat

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SUMMARY

Renal function studies and measurements of in vivo plasma renin activity (PRA), kidney renin content, and renin secretion by isolated, perfused kidneys were performed in spontaneously diabetic and nondiabetic BioBreeding/Worcester (BB/W) rats. Diabetic animals evidenced hyperglycemia, glycosuria, and plasma volume expansion. After dietary sodium deprivation, plasma volume fell to levels equivalent to those of sodium-deprived, nondiabetic rats.

Dietary sodium deprivation evoked a larger proportional increase in PRA among diabetic than nondiabetic animals, although PRA before sodium restriction was equivalent in the two groups.

Basal renin release (RR) was higher from isolated, perfused kidneys from diabetic rats than from nondiabetic kidneys. Diabetic kidneys, moreover, displayed increased kidney renin content (KRC). By contrast, while isoproterenol (10^{-5} M) stimulated a nearly fivefold increment in RR from nondiabetic, perfused kidneys, a negligible effect was observed in diabetic kidneys. The dose-response curve of renin secretion (as a proportion of total renal content) in response to isoproterenol was shifted downward. Hence, while KRC and spontaneous RR by isolated, perfused kidneys were increased, the increment in PRA with salt depletion and the renin-secretory response to isoproterenol in vitro were impaired. We propose that specific defects in renin secretion, in particular, the response to beta-adrenergic stimulation, may be operative in diabetes.

DIABETES 1986; 35:341–46.

The renin-angiotensin system is a central mechanism in the homeostatic control of blood pressure, sodium balance, and glomerular filtration. Renal renin secretion is the primary step in the activation of this hormone system. Both hypo- and hypersecretion of renin have been observed in human diabetes mellitus. Diabetic patients, particularly those with nephropathy, have both low basal PRA[1] as well as a diminished response to stimulation of renin secretion by either isoproterenol infusion[2] or orthostatic tilt.[3] While impaired responses to these stimuli may be due to damage of the juxtaglomerular apparatus by arteriolar hyalinosis and/or glomerulosclerosis,[4] hyposecretion of renin also develops in diabetic patients before the onset of overt renal disease, thus suggesting a basis for the abnormality other than anatomic damage to the juxtaglomerular apparatus.[5] By contrast, increased PRA also occurs in diabetic subjects both with severe hyperglycemia and ketoacidosis[6] as well as in subjects with less severe hyperglycemia.[7]

Diminshed PRA occurs in alloxan-induced diabetes in the rat.[8] Understanding of the pathophysiology underlying the abnormalities of renin secretion has suffered, however, both from a paucity of animal studies and the lack of an ideal animal model. Studies employing alloxan- and streptozocin-induced diabetic models may be confounded by the potential nephrotoxicity of these agents.[9,10]

To explore the basis for the abnormalities of renin secretion in diabetes, we employed the BB/W rat, which develops spontaneous, insulin-dependent diabetes, thus mimicking the syndrome of type I diabetes in humans.[11] PRA in vivo and renin secretion by isolated, perfused BB/W rat kidneys were studied under conditions of normal dietary sodium and after sodium deprivation. Beta-adrenergic stimulation of renin secretion was examined in isolated kidneys from BB/W rats subjected to salt depletion or salt loading.

MATERIALS AND METHODS

Animals. Animals used for these studies were BB/W rats bred and housed at the University of Massachusetts. Approximately 60% of diabetes-prone animals develop a syndrome of insulinopenia, hyperglycemia, and ketosis between 60 and 120 days of age (mean age 90 days).[11] BB/W rats had urine tested twice weekly and diabetic animals were

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Received for publication 4 July 1985 and in revised form 24 September 1985.

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TABLE 1
Renal function parameters in BB/W rats on normal sodium intake

	Diabetics (5)	Nondiabetics (5)	P-Value
Body wt (g)	394 ± 11	404 ± 10	NS
Kidney wt (g)	3.78 ± 0.25	2.83 ± 0.15	<0.02
V (μl/min)	53 ± 9	9 ± 3	<0.0001
RPF (ml/min/g kidney wt)	1.34 ± 0.22	1.67 ± 0.35	NS
GFR (ml/min/g kidney wt)	0.84 ± 0.18	1.00 ± 0.21	NS
Plasma volume (ml/100 g body wt)	3.66 ± 0.37	2.58 ± 0.12	<0.005
Blood sugar (mg/dl)	551 ± 19	139 ± 10	<0.00001
SNa (meq/L)	136 ± 1	140 ± 1	<0.0001
SK (meq/L)	3.9 ± 0.2	3.6 ± 0.1	NS
UNaV (μeq/min)	0.50 ± 0.14	1.04 ± 0.50	NS
UKV (μeq/min)	1.71 ± 0.22	1.56 ± 0.34	NS
FeNa (%)	0.12 ± 0.02	0.22 ± 0.10	NS
FeK (%)	15.1 ± 1.4	14.8 ± 2.2	NS

identified by the appearance of glycosuria and were subsequently given a daily subcutaneous (s.c.) injection of protamine zinc insulin (0.4–2.4 U). The amount of insulin given was sufficient to prevent ketonuria but not glycosuria. Diabetic animals were studied 100–150 days after detection of glycosuria (mean age 217 ± 7 days). Control animals of similar age (216 ± 11 days) were selected from an inbred, "low incidence" strain of nondiabetic BB/W rats (incidence of diabetes <1%).

In vivo studies of renal functional parameters. Separate groups of animals underwent in vivo study while either on a standard diet (Purina rat chow) or on sodium-deficient chow (1 meq Na/100 g, Bio-Serve, Inc., Frenchtown, New Jersey) and ad libitum distilled water. These animals were then anesthetized (pentobarbital 35 mg/kg body wt, i.p.) and the jugular vein, carotid artery, and urinary bladder were catheterized with polyethylene tubing. Animals received a priming bolus of ^{14}C-inulin (0.1 μCi) and ^{3}H-PAH (1.0 μCi) in 0.1 ml of 5% glucose and water followed by a continuous infusion of the two radiopharmaceuticals (0.01 μCi of ^{14}C-inulin and 0.10 μCi ^{3}H-PAH per milliliter) in 5% glucose and water at a rate of 3.0 ml/h. Timed 20-min urine collections were obtained with midpoint blood sampling for determination of the GFR (^{14}C-inulin clearance) and estimated renal plasma flow (^{3}H-PAH clearance), which were calculated by standard formulas. Potassium and sodium concentrations were measured by flame photometry and blood sugar was measured on a Beckman (Fullerton, California) glucose analyzer. After these collections, ^{125}I-albumin was infused for estimation of plasma volume by the method of Ormond and Rivera-Velez.[12]

In vivo study of the effect of sodium deprivation on PRA. Separate groups of unanesthetized animals were pair studied before and after 1 wk of sodium deprivation. Venous tail blood was drawn for determination of plasma renin activity (PRA) before and after 1 wk on the sodium-deficient diet. Samples were collected in chilled tubes with EDTA. PRA was determined by radioimmunoassay for angiotensin I (New England Nuclear, Boston, Massachusetts).[13]

Perfused kidney and in vitro studies. To maximize renin synthesis, all animals subjected to in vitro renal perfusion had received sodium-deficient diets and distilled water for the week before study. To examine the effect of sodium loading, a separate group of animals was fed a high-salt diet (100 meq Na/l00 g, Bio-Serve) and ad libitum distilled water.

The right kidneys were isolated and perfused in vitro by the method of Ross et al.[14] and as described previously.[15–17] Perfusates were prepared with bovine albumin (fraction V, Miles Laboratories, Elkhart, Indiana) made up as a solution with Krebs-Henseleit buffer as described previously.[16] The electrolyte composition of the perfusate was as follows (in millimoles per liter): Na 145, K 4.0, Ca 2.5, Mg 1.2, Cl 103, and HCO_3 25, pH 7.40. Glucose (5 mM) and L-alanine (5 mM) were added at the time of perfusion.

All perfusions were performed at a constant mean pressure

TABLE 2
Renal function parameters in BB/W rats on low-sodium intake

	Diabetics (7)	Nondiabetics (9)
V (μl/min)	57 ± 23	12 ± 5
RPF (ml/min/g kidney wt)	1.08 ± 0.27	1.38 ± 0.22
GFR (ml/min/g kidney wt)	0.58 ± 0.16	0.72 ± 0.13
Plasma volume (ml/100 g body wt)	2.87 ± 0.21*	2.47 ± 0.08*
SNa (meq/L)	125 ± 4	130 ± 3
SK (meq/L)	4.4 ± 0.4	3.6 ± 0.1
UNaV (μeq/min)	0.13 ± 0.06*	0.13 ± 0.03*
UKV (μeq/min)	1.52 ± 0.53	0.67 ± 0.18
FeNa (%)	0.06 ± 0.02*	0.07 ± 0.02*
FeK (%)	18.7 ± 6.0	8.2 ± 1.1

*P < 0.05 versus equivalent group on regular Na intake (Table 1). No significant differences between diabetic and nondiabetic rats on low-Na intake were found for any of the parameters studied.

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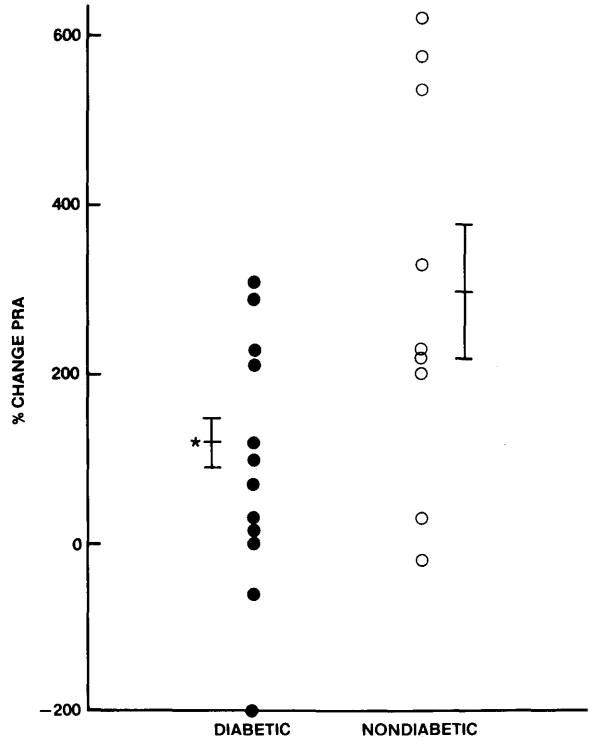

FIGURE 1. Effect of 1 wk of sodium deprivation on the percent change in PRA in diabetic BB/W rats (solid circles) and nondiabetic BB/W rats (open circles). *P < 0.05.

of 120 mm Hg (approximately 90 mm Hg renal artery pressure). Perfusate flow, recorded continuously by an in-line flowmeter, was virtually identical in all experiments.

Kidneys were perfused for 70 min. The first 40 min was allowed for equilibration to permit renin secretion to reach a steady-state level, at which point either isoproterenol (dissolved in a perfusion medium vehicle) was added to the perfusion reservoir to achieve the desired concentration, or no drug was added. Perfusate samples were collected for measurement of renin concentration at the midpoint of each of three subsequent 10-min collection periods (between 40 and 70 min) and averaged. All perfusion experiments were, therefore, compared over the same time interval.

Measurement of perfusate renin concentration was performed by radioimmunoassay for angiotensin I (New England Nuclear) with the addition of dog angiotensinogen substrate as described previously.[15,16] Cumulative perfusate renin concentration was used to derive renin release (RR), which was calculated as reported earlier.[16,17]

At the time of perfusion surgery, the left kidney was removed, decapsulated, weighed, and homogenized. Kidney renin content (KRC) was determined by the method of Boucher et al.[18] and was expressed as micrograms of angiotensin I per gram kidney weight. Both intraassay and interassay variability for angiotensin I were <5%.

Perfusate RR (converted to micrograms of angiotensin I per minute) was expressed as a percent of KRC (micrograms of angiotensin I) as follows: percent KRC released/min = RR/KRC × 100.

Data are expressed as means ± SEM. Statistical differences were determined by Student's *t*-test and by analysis of variance.

RESULTS

In vivo renal function studies. The results of renal physiologic parameters in BB/W rats on a regular diet are presented in Table 1. Body weight in diabetic animals was equivalent to that of nondiabetics. Kidney weight, however, was increased in the diabetic rats.

The diabetic animals were polyuric with a high urine flow (V) presumably reflecting the osmotic diuretic effect of glucose. Both renal plasma flow (RPF) and GFR in diabetic animals were equivalent to the respective values in nondiabetic animals. Plasma volume, however, was significantly expanded in the diabetic rats. Serum sodium (SNa) was slightly but significantly depressed in the diabetic group (136 ± 1 versus 140 ± 1 meq/L in the nondiabetic rats, $P < 0.0001$), presumably owing to the osmotic effect of hyperglycemia, whereas serum potassium (SK) was similar in the two groups.

Physiologic parameters on the low-sodium diet are shown in Table 2. The low-sodium diet caused an overall reduction in plasma volume ($P < 0.05$), UNa V ($P < 0.05$), and FeNa ($P < 0.05$) in both groups of BB/W rats compared with those on a normal diet. However, no differences were observed in these parameters between diabetic and nondiabetic rats. GFR and RPF were approximately equivalent in diabetic and nondiabetic rats. The SNa was also reduced in the sodium-deficient animals, presumably owing to the consequent water retention. Although the SNa was slightly lower in diabetics (125 ± 4 meq/L) than in nondiabetics (130 ± 3 meq/L), this did not achieve statisitical significance.

Serum K, UKV, and FeK were unchanged by the low-sodium diet and were equivalent in diabetic and nondiabetic groups.

Plasma renin activity. In a separate group of experiments, PRA was determined before and after dietary sodium deprivation. The effect of this maneuver in diabetic and nondiabetic BB/W rats is depicted in Figure 1. A significantly larger proportional increment in PRA was observed among nondiabetic rats after sodium deprivation. While diabetic rats increased PRA twofold, sodium depletion induced more than a threefold increase in the nondiabetic group ($P < 0.05$). Basal PRA was, however, similar in the two groups (4.1 ± 0.7 and 2.8 ± 0.5 ng angiotensin I/ml/min, diabetics versus controls, respectively). Likewise, PRA after salt deprivation was similar (8.2 ± 1.1 and 9.1 ± 1.8 ng angiotensin I/ml/min, diabetics versus controls, respectively).

Kidney renin content and basal renin secretion by perfused kidneys. To explore whether defects in renin synthesis or secretory capacity or both were present in diabetics, kidney renin content (KRC) was determined while renin release (RR) was measured in contralateral, perfused kidneys. Kidneys were perfused in vitro without agonist to determine basal secretion.

As is shown in Table 3, KRC was significantly higher in diabetic kidneys removed from animals previously on low- as well as high-salt diets. Kidney renin content was significantly lower in both diabetic and nondiabetic groups on the high-salt intake than on the low-salt intake ($P < 0.0001$).

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TABLE 3
Effect of diabetes on kidney renin content in BB/W rats on low- and high-sodium diets

	Kidney renin content (μg angiotensin I)	
	High-Na diet	Low-Na diet
Diabetic	34.8 ± 4.6 (8)*	68.0 ± 6.3 (20)*
Nondiabetic	16.2 ± 2.9 (11)	48.3 ± 4.6 (20)

*$P < 0.02$ versus nondiabetic.

Basal renin secretion by perfused kidneys from salt-deprived animals was likewise increased in diabetics. As shown in Figure 2, basal RR from diabetic kidneys was significantly higher (36.1 ± 7.2 ng angiotensin I/min) than that from nondiabetics (17.7 ± 2.0 ng angiotensin I/min, $P < 0.03$).

Renin secretion in response to isoproterenol. In contrast to basal renin secretion, the secretory response to the nonspecific beta-agonist, isoproterenol, was significantly impaired in diabetic kidneys from animals subjected to sodium deprivation for 1 wk. As shown in Figure 2, nondiabetic kidneys responded to isoproterenol, 10^{-5} M, with a fivefold increment in RR over basal secretion ($P < 0.001$). Diabetic kidneys, by contrast, failed to respond to isoproterenol and had significantly less renin secretion after this challenge than nondiabetics ($P < 0.05$).

To expand on this finding, renin secretion was studied in response to graded doses of isoproterenol, normalized for kidney renin content and expressed as a percentage of renin content released per minute. The dose-response curves are shown in Figure 3. At low concentrations of isoproterenol, no differences were seen. However, concentrations $>10^{-7}$ M failed to elicit further increases in renin secretion by diabetic kidneys, while renin secretion was significantly greater in nondiabetic kidneys at 10^{-7} M and 10^{-5} M isoproterenol concentrations.

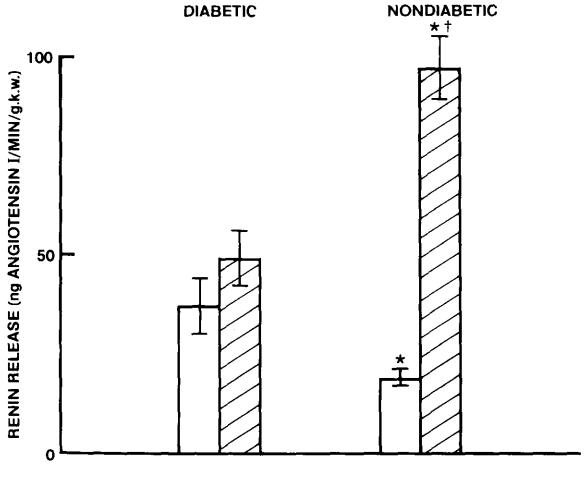

FIGURE 2. Rate of renin release by isolated, perfused kidneys from diabetic and nondiabetic BB/W rats. Renin release is expressed as nanograms of angiotensin I units released per minute per gram kidney wet weight. Basal perfusions (open bars) are those without agonist in the medium. Isoproterenol-stimulated perfusions (hatched bars) are those with agonist added to the perfusate (10^{-5} M). *$P < 0.05$ versus comparable perfusions in diabetic kidneys. †$P < 0.001$ versus control perfusions in nondiabetic kidneys.

Isoproterenol (10^{-5} M)-stimulated renin secretion was also examined in animals placed on a high-salt diet. The percentage of renin content released per minute was reduced overall by high-salt intake ($P < 0.05$). Isoproterenol-stimulated renin secretion (normalized for KRC) was 0.20 ± 0.01%/min in nondiabetics and 0.07 ± 0.01%/min in diabetics on low-sodium intake ($P < 0.0001$). By contrast, on high-sodium intake, nondiabetic kidneys released 0.12 ± 0.02%/min, while diabetics released only 0.04 ± 0.01%/min ($P < 0.02$).

The relationship between isoproterenol-stimulated RR and KRC is shown for both diabetic and nondiabetic kidneys in Figure 4. The data from animals on high- and low-salt diets were pooled and are shown together. RR induced by isoproterenol was dependent on preexisting KRC, the significance of this relationship being demonstrated by the high correlation coefficients for both diabetic and nondiabetic groups. However, significantly different lines could be plotted for diabetic and nondiabetic kidneys, as revealed by analysis of variance of slopes and intercepts ($F = 16.3$, $P < 0.00001$). Consequently, for any given KRC, isoproterenol-stimulated RR was lower in the diabetic group.

DISCUSSION

The BB/W rat was selected for use in this study because it is a model of spontaneous diabetes that closely resembles type I diabetes in man.[11] Most previous animal studies of the renin-angiotensin system have employed the use of alloxan or streptozocin, agents whose potential nephrotoxicity may confound these studies.[9,10] Our initial morphologic and functional observations of diabetic BB/W rats demonstrate typical early features of diabetic glomerulopathy, including proteinuria and glomerular basement membrane thickening.[19]

The renal physiologic parameters of BB/W rats on regular sodium intake demonstrate increased plasma volume and urine flow. Kidney weight was significantly increased, as reported in other animal models of diabetes.[8,22] The plasma volume expansion and polyuria are presumably related to the osmotic effect of glucose both to expand the extracellular fluid volume and to induce a diuresis. Although other reports have suggested that early diabetes is associated with increased GFR and RPF,[20,21] our results show that GFR and RPF are equivalent in severely hyperglycemic diabetic and nondiabetic animals and are consistent with the study of Hostetter et al.,[22] who demonstrated that GFR is lower in rats with more severe hyperglycemia. BB/W diabetic animals in our study had blood sugars of 500–600 mg/dl (Table 1), similar to the "severely hyperglycemic" group in the paper by Hostetter et al.[22] Why these animals do not display glomerular "hyperfiltration" is not clear. Further studies will be necessary to evaluate the impact of glycemic control on renal function in the BB/W rat model.

Our study reports results for PRA and KRC that differ from those of Christlieb.[8] Both the duration as well as the severity of hyperglycemia in our study closely approximated those reported by Christlieb in alloxan-diabetic rats.[8] As was also the case in both alloxan- and streptozocin-treated rats,[8,22] plasma volume was elevated in spontaneously diabetic animals. Christlieb, however, reported that both PRA and KRC were diminished in alloxan-diabetic rats, in contrast to the present findings. Whether the differences in these studies

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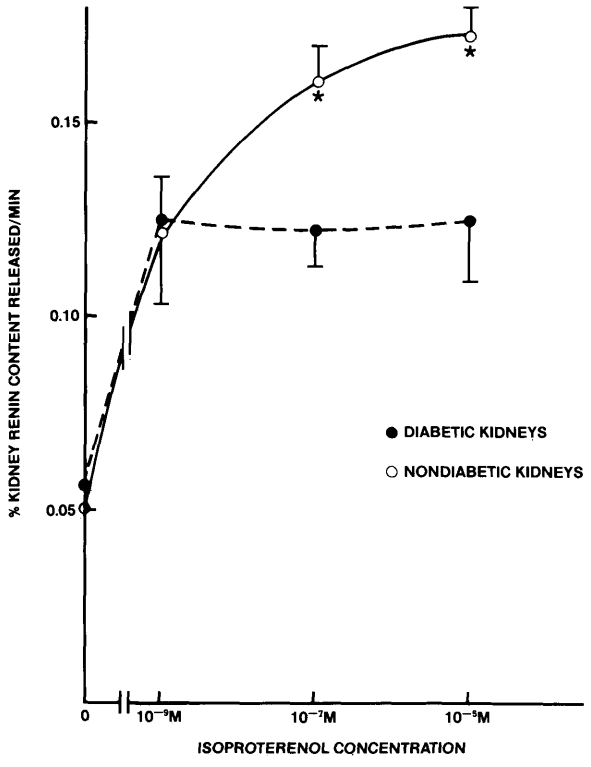

FIGURE 3. Dose response of percent of kidney renin content released per minute by isolated kidneys versus concentration of isoproterenol added to the perfusate. N = 8 in each group at each dose. *P < 0.05 versus diabetic kidneys.

can be explained by a direct effect of alloxan on renin-secreting cells requires further elucidation. It is noteworthy, however, that PRA in the spontaneously diabetic BB/W rat is similar to that observed in human subjects with diabetes in whom unstimulated PRA is generally normal or elevated.[7,8]

Diabetic and nondiabetic animals on sodium-deficient diets showed equivalent plasma volume, GFR, RPF, UNaV, and FeNa. Renin secretion is mediated by a renal baroreceptor sensitive to extracellular fluid volume, the macula densa (which senses tubular solute delivery), and sympathetic nerves and catecholamines. The similarity of the RPF and plasma volume indicates that the renal baroreceptor was equally activated in diabetic and nondiabetic animals subjected to dietary sodium deprivation. Likewise, similarity in UNaV and FeNa suggests that the macula densa signal was not substantially different in the two groups. Nonetheless, the increment in PRA was smaller in a group of diabetic animals subjected to sodium depletion. Hence, although basal PRA was equivalent to that of nondiabetic rats and despite increased kidney renin content, the response to salt deprivation was proportionately smaller in diabetic rats, thus suggesting a defect in one or several renin secretion mechanisms. The "normal" basal PRA in diabetic animals presumably having increased intrarenal renin may also suggest defective renin secretion. Similar findings have been reported in patients with diabetes in whom basal PRA is equivalent to that of control subjects, but in whom the responses to orthostasis,[3] furosemide,[23] or isoproterenol[2] are subnormal.

The sympathoadrenal system plays a key role in mediating renin secretion in response to hemorrhage, anesthesia, orthostasis, and acute sodium depletion.[24] Because of the primacy of beta-adrenoreceptors in the augmentation of renin secretion, we studied the renin secretory response to isoproterenol, a nonspecific beta-agonist, in isolated, perfused BB/W rat kidneys. Both the absolute rate of renin secretion as well as the percentage of available renin stores released by diabetic kidneys under the influence of isoproterenol were smaller when compared with nondiabetics. This finding confirms a recent study in alloxan-diabetic mice in which isoproterenol-stimulated PRA was attenuated.[25] It also parallels the finding that human diabetic subjects have negligible renin release in response to intravenous isoproterenol compared with control subjects.[7] Furthermore, the subnormal response to orthostatic tilt observed in diabetic subjects,[28] a finding attributable to a disordered sympathoadrenal system, may be on a similar basis.

However, unlike previous studies in alloxan-diabetic rats,[8,25] PRA was not decreased and both KRC and basal renin secretion by perfused kidneys was consistently increased among our diabetic animals. Furthermore, spontaneous, unstimulated RR by diabetic perfused kidneys was also larger than in nondiabetic kidneys. The increased KRC in diabetic BB/W rats may be due to either diminished renin secretion or enhanced renin synthesis; the results of the present study do not permit further interpretation of this finding.

A specific impairment of beta-adrenergically stimulated renin secretion is suggested by our studies. Unstimulated RR was unimpaired in diabetic animals, whereas isoproterenol-stimulated RR was attenuated. The diminished increment in PRA in response to salt deprivation may also be a manifestation of a defect in the beta-adrenergic system.[24] Along similar lines, defects in the beta-adrenergic control

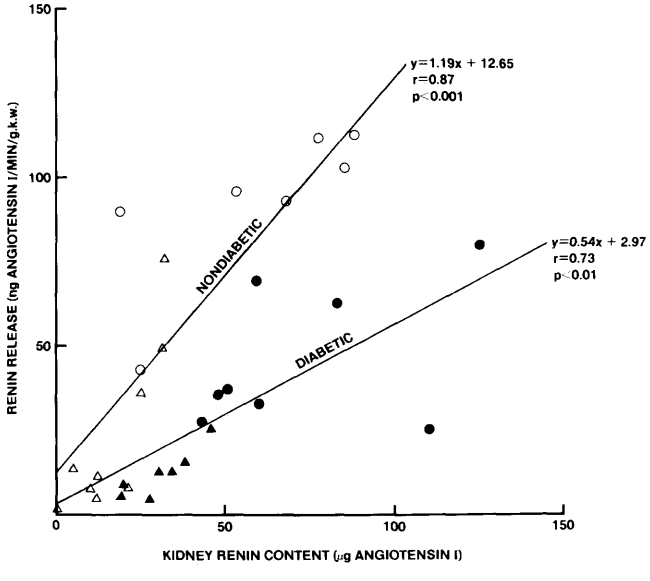

FIGURE 4. Regression plot of isoproterenol (10^{-5} M)-stimulated renin release by isolated, perfused kidneys versus kidney renin content from contralateral kidneys harvested from the same diabetic (solid symbols) or nondiabetic (open symbols) BB/W rats. Animals previously on high-salt diets are represented by the triangles. Those from animals on low-salt diets are represented by the circles. Significance of the regression lines is shown by the r-values. Analysis of variance of the regression lines for diabetic and nondiabetic kidneys showed that both the slopes and y-intercepts were different (F = 16.3, P < 0.0001).

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have been identified in other tissues in animals with diabetes. For example, the bradycardia observed in streptozocin-diabetic rats is associated with a decrease in the number of cardiac ventricular beta-adrenoreceptors, suggesting that the negative chronotropic effect of diabetes is on the basis of diminished beta-adrenergic drive.[26] Whether a decrease in renal renin-mediating beta-adrenoreceptors occurs in diabetes remains to be determined. Diminished renal vasoconstriction in response to the alpha-adrenergic agonist, norepinephrine, has been observed in isolated, perfused, diabetic rabbit kidneys,[27] suggesting that a more generalized abnormality in adrenoreceptor regulation may be present.

Elucidating the effects of diabetes on the adrenergic system is central to an understanding of impaired cardiovascular homeostasis in human diabetes. Diminished sensitivity to beta-adrenergic stimulation may contribute to orthostatic hypotension in diabetic subjects. Although autonomic neuropathy and impaired catecholamine synthesis have been proposed to explain this phenomenon,[28] plasma catecholamines in diabetic patients with orthostasis may be normal or even elevated.[29] Hence, a defect "distal" to neuronal catecholamine release may be operative, which results in both hyposecretion of renin and impaired vascular reactivity.

The seemingly paradoxical findings of hyposecretion of renin under some conditions and hypersecretion in others in diabetic patients might be explicable by a defect in beta-receptor–mediated renin secretion, while other mechanisms responsible for renin secretion, such as the renal baroreceptor, may be intact. The possibility that nonadrenergically controlled renin secretion is intact is also suggested by observations that PRA is increased in patients with "uncomplicated" diabetes[8] and in those with retinopathy.[30] PRA is also increased in ketoacidosis[7] and after diazoxide infusion,[31] both of which may stimulate renin secretion by a nonadrenergic baroreceptor mechanism. Further studies will be necessary to examine whether the responses to other renin secretagogues are intact in diabetes.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the clerical skills of Judith Konan and also wish to thank Dr. Jeffrey S. Stoff for his advice and help with this manuscript.

This work was supported by a Diabetes Endocrine Research Center grant from the NIH (1P30-AM-32520).

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