Altered Regulation of Renin Secretion by Insulinlike Growth Factors and Angiotensin II in Diabetic Rats

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The etiology of the low renin state in DM is not clear. To assess the role of certain growth and regulatory factors in this process, we studied the effects of insulin, IGF-I, and IGF-II on the renin-angiotensin system in normal and 8-wk STZ-induced diabetic rats. Renin secretion was studied both in static incubations and by perifusion of rat renal cortical slices. In diabetic rats, both plasma renin activity (0.65 ± 1.6 vs. 4.0 ± 1.2 ng ANG I · ml^{-1} · h^{-1}) and tissue renin concentrations (27 ± 5 vs. 51 ± 8 ng ANG I · mg $tissue^{-1}$ · h^{-1}) were reduced. Insulin (0.1–1.0 mu/ml) and IGF-I (10^{-9} to 4×10^{-9} M) stimulated renin secretion in normal tissue (control, 95 ± 3%; insulin [0.5 mu/ml], 134 ± 7%; IGF-I [4×10^{-9} M], 149 ± 7%). IGF-I stimulated renin secretion in perifusions as early as 30 min, whereas IGF-II had no effect. However, in diabetic renal tissue, neither insulin (0.1–1.0 mu/ml) nor IGF-I (10^{-9} to 4×10^{-9} M) had an effect on renin. This lack of effect was overcome by adding up to 100-fold higher concentrations of these growth factors. ANG II (10^{-10}M–10^{-8} M) had an exaggerated inhibitory effect on renin secretion in diabetic tissue. This study suggests that the low renin state in DM may be explained by the enhanced inhibitory effect of ANG II and the resistance to the secretogogue actions of insulin and IGF-I. *Diabetes* 41:1100–05, 1992

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DM, diabetes mellitus; IGF-I, insulinlike growth factor I; IGF-II, insulinlike growth factor II; STZ, strepzotocin; ANG II, angiotensin II; ANG I, angiotensin I; KRBG, Krebs-Ringer bicarbonate with glucose; BSA, bovine serum albumin; ANOVA, analysis of variance; VSM, vascular smooth muscle.

DM, especially DM with nephropathy, generally has been considered a low renin state (1), and a subgroup develops hyporeninemic hypoaldosteronism (2–4). However, the mechanism(s) for the low renin state of DM have not been well documented or explained. A relative block in processing prorenin to the active form and reduced secretion of renin after stimulation suggests the possibility that local factors or feedback abnormalities may be involved in inhibiting renin secretion in DM (2–5).

This study was designed to evaluate tissue and circulating renin in an animal model of DM, the STZ-induced diabetic rat. We studied the feedback action of ANG II in vitro in the diabetic and normal rat. Because insulin has been reported to increase renin levels in humans (6,7), we studied the effect of insulin and insulinlike peptides on renin secretion in vitro, in both normal and diabetic rats.

RESEARCH DESIGN AND METHODS

Studies were carried out in male Sprague-Dawley rats weighing 180–220 g. DM was induced by a single injection of 45 mg/kg STZ, freshly dissolved in citrate buffer, pH 4.5, into the tail vein of rats. Age- and/or weight-matched control rats were given a similar injection of citrate buffer alone. The rats were maintained on a normal diet and water ad libitum. In general, rats were diabetic within 48 h, as assessed by plasma-glucose levels, and they were studied 8–10 wk after STZ or buffer treatment.

Methods. Renal cortical slices (0.5 mm thick) were prepared for static incubations and perifusion experiments (Endotronics Acusyst S Perifusion System, Marietta, OH) by a method described previously (8–10). For static incubations, slices (15–30 mg) were washed with KRBG medium containing 0.2% BSA. Slices then were preincubated in a metabolic shaker, saturated with 95%

O_2–5% CO_2 at 37°C for 30 min, and incubated for two consecutive 30-min periods. Each slice was incubated for a 30-min baseline period, after which various agents were added. The response to an agent was observed for the next 30-min period, thus enabling each slice to serve as its own control. The standard KRBG medium contained (in mmol concentrations): 120 NaCl, 4.7 KCl, 1.2 $MgSO_4$, 2.5 $CaCl_2$, 1.2 KH_2PO_4, 26.8 $NaHCO_3$, and 10 glucose, pH 7.4. For perifusions, slices were placed in culture chambers and perifused with KRBG buffer at a flow rate of 0.5 ml/min, as described previously (10). After an initial 60-min stabilization period, 5-min fractions were collected. After a 30-min baseline sampling, the agents were dissolved in 30 ml KRBG buffer and perifused over a 30-min period. This was followed by a control KRBG buffer for a 30-min period.

Insulin and ANG II were dissolved in KRBG buffer with 0.2% BSA and freshly prepared on ice just before use. IGF-I and IGF-II were prepared in 0.1 M sterile glacial acetic acid at the concentration of 50 μg/ml and then diluted to a required molar concentration with KRBG buffer with BSA. Renin activity in the plasma or renin concentration in the supernatant of the incubations or perifusion medium were determined as described previously (8–10). Briefly, 5–10 μl aspirated medium were incubated with 50 μl rat plasma containing an excess of renin substrate, prepared from nephrectomized rats according to the method of Skinner et al. (11). The substrate solution also contained 5 μl dimercaprol (2% solution [wt/vol] of benzyl benzoate, Sigma, St. Louis, MO), 10 μl 8-hydroxyquinoline sulfate (0.17 M), 25 μl EDTA-2Na (4%), and 110 μl Tris-lysozyme buffer, pH 7.4. The mixture was incubated for 1 h at 37°C and ANG I generation was measured by radioimmunoassay by the method of Haber et al. (12), with modifications (8–10). Similarly, renin activity in the plasma was measured without added substrate. In the static incubation model, renin release during the second 30-min incubation was expressed as the percentage of basal release in the same slice during the first 30-min period. In the perifusion experiments, renin release during each collection period was expressed as the percentage of basal release in the same chamber during the first collection period (0-10 min).

Materials. Human recombinant IGF-I and IGF-II were obtained from Bachem (Torrance, CA). ANG II was obtained from Peninsula Labs, (Belmont, CA) and human insulin from Eli Lilly (Indianapolis, IN). STZ came from Upjohn diagnostic (Kalamazoo, MI). Pentex BSA (fatty acid-free fraction v) was obtained from Miles Laboratories (Naperville, IL).

Statistical significance was determined with ANOVA, unpaired Student's *t* tests, and a multiple comparison method (using either Duncan's or Dunnett's test wherever appropriate), as described previously (8–10). For perifusion experiments, the area under the curve was subjected to one-way ANOVA using Dunnett's method.

RESULTS

Plasma glucose levels in the diabetic rats at the time of death were elevated significantly compared with controls

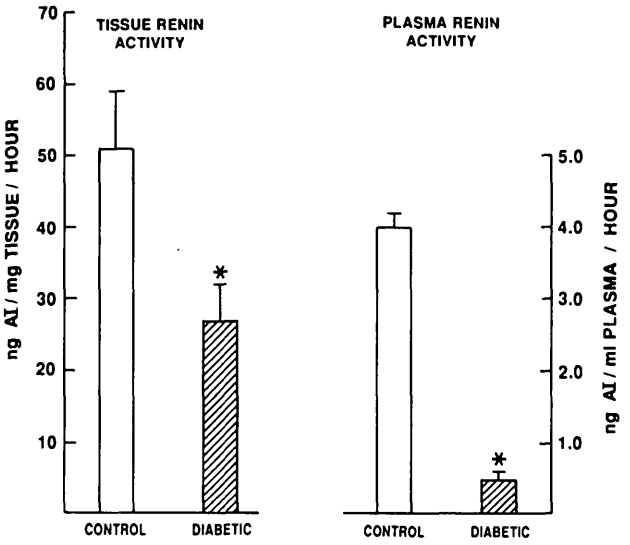

FIG. 1. Plasma renin activity and renal tissue renin concentration in control (□) and STZ-induced diabetic (▨) rats. Renin activity or renin concentrations were determined as indicated in text. Each value represents the mean ± SE from 8–10 animals.

(22.3 ± 2.8 vs. 7.8 ± 0.6 mM, $P < 0.001$). During the course of the study, the normal rats gained 200 ± 4–380 ± 6 g, whereas the diabetic rats did not gain weight. Despite their lack of weight gain overall, the kidney weight of the diabetic rats (4.5 ± 0.5 g) was twofold higher than the kidney weight of the normal rats (2.2 ± 0.4 g). Plasma renin activity and tissue renin concentrations in control and diabetic rats were determined at the time of death. The plasma renin activity of the diabetic rats (0.65 ± 1.6 ng ANG I · $ml^{-1} \cdot h^{-1}$) was significantly lower than control rats (4.0 ± 1.2 ng ANG I · $ml^{-1} \cdot h^{-1}$) $P < 0.001$. Similarly, the basal renal renin concentration/mg of tissue in the diabetic rats also was lower than control rats (27 ± 5 vs. 51 ± 8 ng ANG I · mg $tissue^{-1} \cdot h^{-1}$) (Fig. 1).

However, total renal renin content was not reduced in diabetic rats compared with controls when corrected for kidney weight, because the weight of the kidney doubled in diabetic animals.

Effects of insulin and IGF-1 on renin release in normal and diabetic renal tissue. Renin secretion by the cortical slices was relatively stable during two consecutive 30-min periods (1st period, 14.9 ng ANG I · mg $tissue^{-1} \cdot h^{-1}$ [100%]; 2nd period, 14.3 ng ANG I · mg $tissue^{-1} \cdot h^{-1}$ [96%]). The absolute levels of renin release exhibited considerable variation between incubations, even when corrected for slice weight as noted previously (8). Values within the same slice did not differ greatly. This finding emphasizes the importance of using each slice as its own control.

In static incubations, insulin administered at 0.1 mu/ml increased renin slightly (Fig. 2), but 0.5 mu/ml (3.5×10^{-9} M) insulin significantly increased renin secretion in normal rats compared with control slices (control, 95 ± 3%; insulin, 0.5 mu/ml, 134 ± 7%; $P < 0.001$). A higher concentration (twofold) did not further stimulate renin release. Recombinant IGF-I, like insulin, also stim-

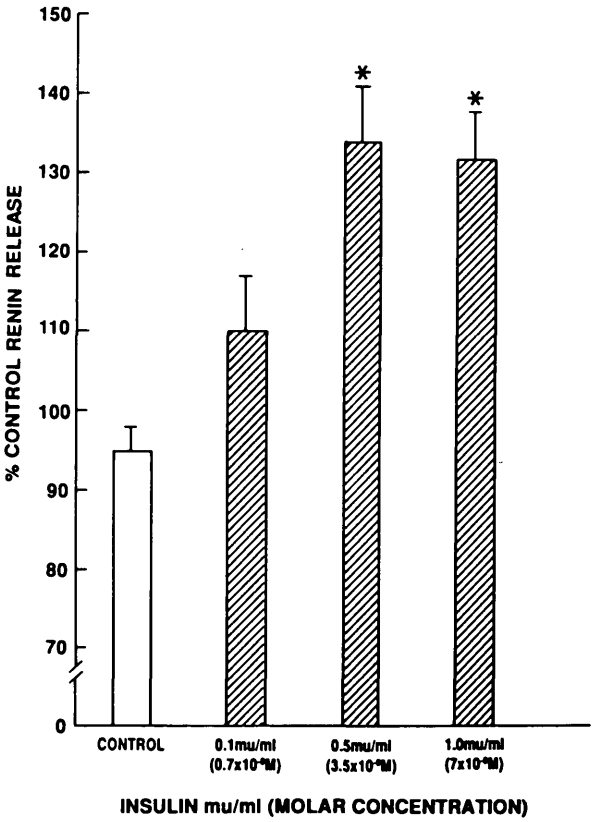

FIG. 2. Renin release from rat renal cortical slices in control incubations (□) and after insulin stimulation (▨). Incubations were performed as indicated in text. The effect of insulin is expressed as a percentage of baseline at 30 min. Values are means ± SE representing 7–8 experiments. Insulin (0.5 mu and 1 mu/ml) significantly stimulates renin release. *$P < 0.001$

ulated renin secretion markedly. As little as 4×10^{-9} M concentration significantly stimulated renin secretion to 149 ± 7% (Fig. 3). In contrast, IGF-II at concentrations from 10^{-10} to 10^{-8} M had no effect on basal renin release.

To further characterize the action of IGF-I, we studied the time course of stimulation during perifusion. Renin release in control slices was relatively stable over the entire 60-min period. IGF-I stimulated renin secretion significantly over the control slices after 20 min (Fig. 4).

In diabetic renal tissue in static incubations, neither insulin (0.1–1 mu/ml) nor IGF-I (10^{-9} to 4×10^{-9} M) had an effect on renin secretion. Figure 5 indicates a representative study with insulin 7×10^{-9} M and IGF-I, 4×10^{-9} M concentration (control 93 ± 4% vs. diabetic 85 ± 3% and 85 ± 2%, respectively). This effect was overcome by adding 20- to 100-fold higher concentrations of the peptides (control 100 ± 4%, insulin 20 mu/ml, 129 ± 6%; IGF-1 10^{-7} M, 133 ± 8%, both $P < 0.01$).

Elevations of glucose in the media up to 27.8 mM (500 mg/dl) did not modify renin release of normal or diabetic tissue (normal 104 ± 10 vs. 105 ± 8% diabetic).

Effects of ANG II on renin release in normal and diabetic renal tissue in static incubations. ANG II added to control tissues caused an inhibition of renin release in a dose-dependent manner. A 10^{-10} M dose of ANG II did not affect renin secretion (basal 100 ± 4%;

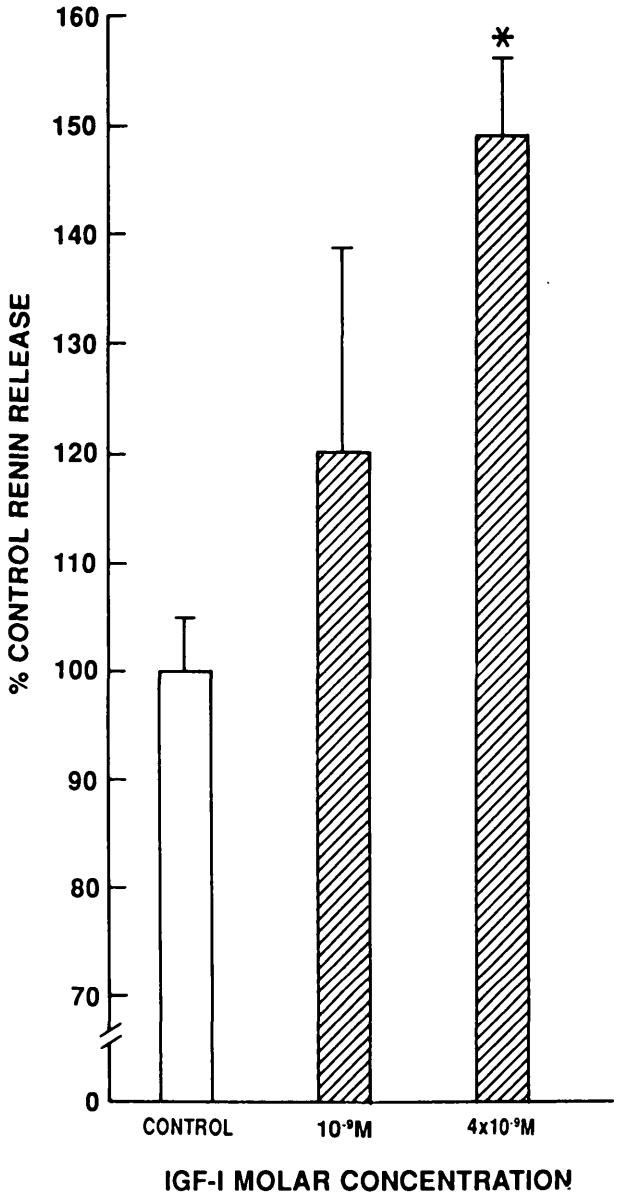

FIG. 3. Effects of recombinant IGF-I on renin release by rat renal cortical slices at 30 min. Each value represents the mean ± SE of 6–8 experiments. Control, (□); IGF-I, 4×10^{-9} M (▨) significantly stimulates renin secretion compared with control slices. *$P < 0.001$

ANG II, 10^{-10} M 99 ± 5%); 10^{-9} M ANG II reduced renin slightly to 91 ± 4%, whereas 10^{-8} M ANG II decreased renin release significantly to 79 ± 5%, $P<0.01$. A higher concentration (10^{-7} M) did not further decrease renin (79 ± 5%).

In contrast, the diabetic renal tissue was much more sensitive to ANG II, requiring only 1/100th (10^{-10} M) concentrations to significantly decrease renin release (control 99 ± 4%, ANG II 10^{-10} M 77 ± 3%, $P<0.02$). Further inhibition occurred at concentrations of 10^{-9} (75 ± 5, $P < 0.01$) and 10^{-8} M ANG II (61 ± 3%, $P < 0.001$). The shift of the dose-response curve to the left is shown in Fig. 6.

DISCUSSION

The regulation of renin secretion is complex and the result of numerous factors including angiotensin feed-

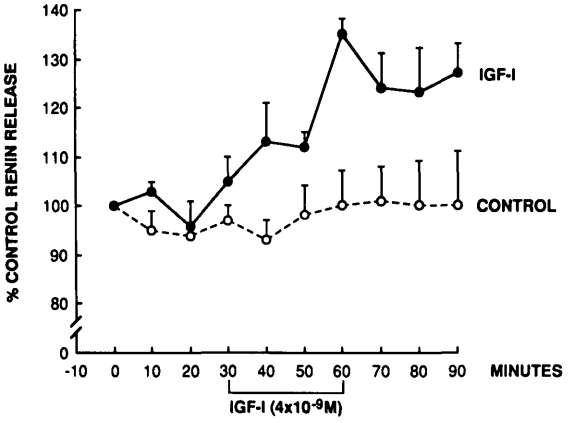

FIG. 4. Renin secretion in perifused rat renal cortical slices. Time course and effects of IGF-1 on renin secretion. Perifusions were performed as indicated in text. Results are expressed as the percentage of each basal renin release during the first 0–10 min. Values are means ± SE of 6–7 different experiments. One-way ANOVA was performed on the area under the curve, and statistical significance was found between groups at $P = 0.005$.

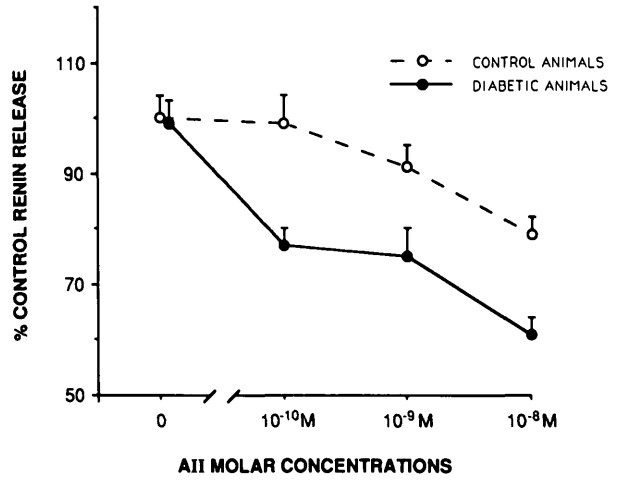

FIG. 6. Dose-related inhibitory effects of ANG II on renin release by rat renal cortical slices from control and diabetic rats. Values are means ± SE, representing 12–14 experiments. Diabetic tissue was more sensitive to ANG II, showing greater inhibition and shift in the dose-response curve to the left.

back, potassium, sodium, and sympathetic activity (catecholamines) (13,14). Additionally, it is possible that local paracrine factors may play a role. Because renin secreting cells are derived from VSM, (15) it is not surprising to discover that certain growth factors or cytokines might modulate renin synthesis and secretion. VSM cells secrete IGF-I, and recent reports indicate IGF-I gene expression in these cells (16). Therefore, we studied the status of angiotensin feedback, and the effect of insulin and IGF peptides on renin secretion in vitro in normal and STZ-induced diabetic rats.

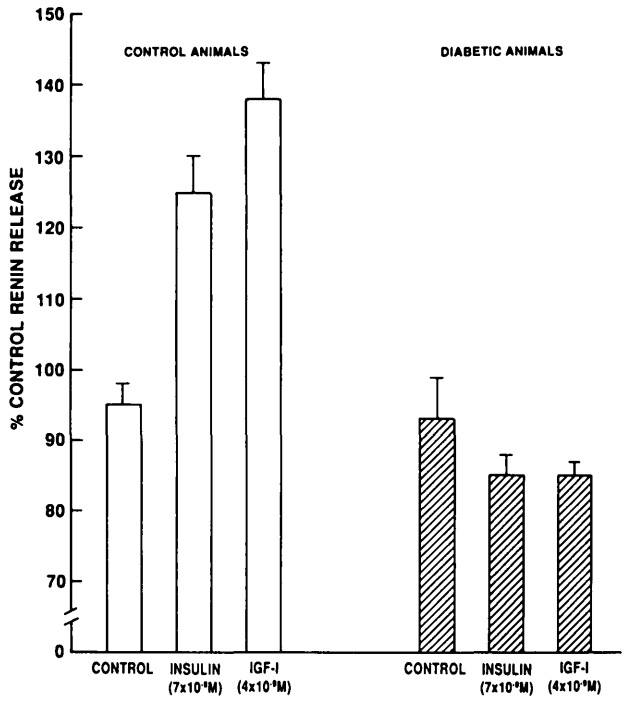

FIG. 5. Effects of insulin and IGF-I on renin secretion from control (□) and STZ-induced diabetic (▨) rats. Results are expressed as mean ± SE, representing 8–10 experiments. In control rats, both insulin and IGF-I significantly stimulated renin secretion, *$P < 0.001$. In diabetic rats, neither insulin nor IGF-1 at the dose used had an effect on renin secretion. A much higher dose stimulates renin secretion (not shown).

Insulin in nmol concentrations is a potent renin stimulator. This agrees with in vivo literature in humans (6,7), dogs (17), and rats (18). The only available in vitro study reached a different conclusion (19), perhaps because their animals were on a low sodium diet, which increases both basal renin secretion and reduces ANG II receptor binding (20,21). In another study in humans, Lowder et al. (22) found that only those patients with normal basal renin levels responded to insulin.

Our study also reports for the first time that nmol concentration of recombinant IGF-I also stimulates renin secretion. This can be demonstrated in both static incubations and perifusions. The latter is considered more physiological because the products from slices and medium are washed out continuously, and the contents of the medium are kept constant. In addition, perifusions studies indicate the time-course action of an agent. It can be seen that IGF-I induces renin release very rapidly (minutes). This action of IGF-I can be demonstrated at concentrations similar to those inducing other endocrine effects such as altering steroid aromatase activity in ovary (23) and enhancing luteinizing hormone effects on testosterone production by Leydig cells (24). In contrast, IGF-II doses in the range 10^{-10}–10^{-8} M had no effect on renin secretion.

The degree of stimulation with IGF-I was approximately the same as that of insulin. Although, it is now clear that cellular components that regulate and mediate the biological responses of insulin and IGF-I share several levels of structural and functional homologies and are highly integrated (25). IGF-I probably acts at this dosage through its own receptors, because in renal glomeruli the competitive binding of insulin with IGF-I receptors occurs only at micromolar concentrations (26).

It is clear that these rapid effects are not caused by mitogenesis and growth per se, and suggest that this is

an effect on stored renin or by activating mechanisms of conversion of inactive to active renin (27). A number of alterations in the regulation of renin can be demonstrated in this diabetic rat model. In confirmation with other studies in diabetic humans and animals (1,28,29), we find that both plasma and tissue renin activity (calculated per ml or mg of tissue) is much lower than nondiabetic age- and weight-matched controls. Damage to glomeruli and juxtaglomerular cells could explain these observations; although detailed morphometric analysis was not done, no pathological findings were noted under light or electron microscopy. A significant increase in kidney weight (both absolute and relative) was observed in our diabetic rats, but the effective renin secretion was lower because plasma renin activity was low. STZ, at the dose used, does not cause detectable renal injury (30) and direct addition of STZ (10^{6}–10^{-5} M) to kidney tissue had no effect on renin release.

Another possibility is that the lowered levels of renin or altered responsiveness could be caused by hyperglycemia per se. However, we have shown that elevations of glucose in media in levels up to 27.8 mM (500 mg/dl) do not modify the renin responses of normal or diabetic tissue.

Another striking observation is the increased response to ANG II, with a ~100-fold shift of the dose response to the left. This effect has been observed in vivo where angiotensin induces a greater rise in blood pressure in DM (31,32), although this type of hypersensitivity also is seen in low renin states.

A number of possibilities exists whereby angiotensin produces an enhanced vascular/renin action. Angiotensin action is expressed through the calcium diacyglycerol-protein kinase-C messenger system (33,34), and some evidence has been found for increased intracellular calcium in diabetic vascular tissue (35–36). Angiotensin may exert some of its effects via calcium and phospholipase activation and production of arachidonic acid, a precursor of various vasoactive prostaglandins (33,34,10). An alteration in the major pathways of prostaglandin formation has been reported from diabetic vessels and kidney (37–39). Because certain members of this family are renin secretogogues (9,40,41) or inhibitors (9,42), altered regulation of renin could be caused by changes in the second messenger status in DM.

Glomerular angiotensin receptors also are reduced initially in diabetic rat models, however, by 8 wk after STZ-induced DM, near normal receptor density is observed (43).

In diabetic renal tissue, the renin response to either insulin or IGF-I is blunted, and the dose response is shifted to the right. Resistance to insulin and IGF-I has been demonstrated previously in other tissues, such as in muscle in obese human subjects and animals with or without DM (44–46), and our observation may be another example of insulin and IGF-I resistance in the diabetic state.

The mechanisms whereby insulin or IGF-I acts on renin secretion are not known. Possibilities of insulin effects include actions on adrenergic receptors (7,13,47), prostaglandin formation (48), or decreased potassium concentrations (49). Insulin and IGF-I can act on some cells via activation of tyrosine kinase, protein phosphorylation, and the protein kinase C systems (50). IGF-I can alter calcium flux (51) and phospholipid synthesis (52,53). Changes in these potential intracellular messengers potentially could alter renin synthesis and secretion (8,13, 14).

The kidney is an abundant source of IGF-I (54,55). IGF not only promotes growth but also may affect renal functions in a paracrine fashion. Although renal IGF-I tissue levels are reduced in DM, both IGF-I binding proteins I and II mRNA and IGF-I receptor mRNA are increased in diabetic kidneys (56,57). IGF-I action is modified by the various IGF binding proteins (56) and increased binding protein formation by diabetic kidney could account for the relative resistance demonstrated by our studies. However, this would not account for the resistance to insulin and the increased inhibitory action of ANG II.

Therefore, we believe that the low renin state (blood and tissue) of experimental DM appears to be a combination of factors involving endocrine (insulin resistance) and paracrine (IGF-I) factors, and renin vascular hypersensitivity to ANG II feedback. These alterations may be part of a larger derangement in vascular responsiveness that is associated with the hypertension and vasculopathy of DM.

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