Renal Kallikrein and Hemodynamic Abnormalities of Diabetic Kidney

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The relationship between renal hemodynamic abnormalities and renal kallikrein activity was studied in streptozocin-induced diabetic rats. Diabetic rats were either not treated with insulin and had plasma glucose levels >400 mg/dl (severely hyperglycemic diabetic [SD]) or were treated with 1.5–1.75 U/day protamine zinc insulin and had glucose levels of 200–300 mg/dl (moderately hyperglycemic diabetic [MD]). In SD rats, kidney tissue level and excretion of active kallikrein were reduced after 3 wk compared with age-matched nondiabetic control rats (tissue, 11.7 ± 1.9 vs. 20.5 ± 1.8 ng/mg protein, $P < 0.005$; urine, 126 ± 12 vs. 179 ± 10 μg/24 h, $P < 0.005$). Despite increased kidney size, renal plasma flow (RPF) was reduced in SD rats (5.38 ± 0.23 vs. 6.37 ± 0.20 ml/min, $P < 0.05$). Glomerular filtration rate (GFR) was not significantly lower (2.77 ± 0.60 vs. 3.02 ± 0.56 ml/min). In MD rats, kidney tissue level and excretion of active kallikrein were increased after 5 wk compared with age-matched nondiabetic control rats (tissue, 28.4 ± 1.3 vs. 23.3 ± 1.7 ng/mg protein, $P < 0.05$; urine, 289 ± 16 vs. 196 ± 13 μg/24 h, $P < 0.001$). In MD rats, GFR and RPF were increased (3.80 ± 0.11 and 8.04 ± 0.17 ml/min, respectively) compared with control rats (3.22 ± 0.05 and 7.28 ± 0.09 ml/min, $P < 0.001$). Treatment of MD rats with a kallikrein inhibitor reduced GFR and RPF to levels similar to those of nondiabetic control rats. With recent evidence that kallikrein and kinins have a renal paracrine role in regulating vascular resistance, our findings suggest that altered kallikrein activity may contribute to the renal hemodynamic and filtration abnormalities in diabetes. *Diabetes* 39:299–304, 1990

Glomerular hyperfiltration has been identified as a predictor of the subsequent development of nephropathy in patients with insulin-dependent diabetes mellitus (IDDM) (1). Glomerular hemodynamic measurements in moderately hyperglycemic streptozocin-induced diabetic (STZ-MD) rats show that increased filtration pressure and increased glomerular plasma flow, which together produce hyperfiltration, are due to imbalanced dilation of afferent and efferent glomerular arterioles (2). Studies in the same model suggest that the raised filtration pressure contributes to glomerular damage (3,4). In contrast to these hemodynamic changes in insulin-treated MD rats, untreated severely hyperglycemic diabetic (SD) rats show glomerular arteriolar vasoconstriction and reduced glomerular flow, filtration pressure, and glomerular filtration rate (GFR) (2).

Several studies have examined the possible role of endocrine and paracrine factors in producing these hemodynamic changes. One study suggested that raised plasma atrial natriuretic peptide (ANP) levels increase GFR in streptozocin-induced diabetic (STZ-D) rats, but clinical studies have not confirmed this (5–7). An early study showed increased glomerular synthesis of vasodilator and vasoconstrictor eicosanoids in hyperfiltering diabetic rats (8). However, a recent report claims the ratio of these eicosanoids favors vasodilation in hyperfiltering STZ-MD rats and vasoconstriction in severely hyperglycemic rats with reduced GFR (9). Treatment with an angiotensin-converting–enzyme inhibitor lowers filtration pressure in hyperfiltering rats but does not reverse glomerular arteriolar dilation, hyperperfusion, or hyperfiltration (4).

Accumulated data suggest that the renal kallikrein-kinin system has a paracrine function to regulate glomerular hemodynamics (10–12), and interactions have been described between renal kallikrein, kinins, eicosanoids, ANP, and the renin-angiotensin system (13–17). We previously reported that insulin-treated IDDM patients show increased kidney excretion of active kallikrein (18), whereas untreated severely hyperglycemic streptozocin-induced diabetic (STZ-

Glucose 1 mM = 18 mg/dl

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Received for publication 6 April 1989 and accepted in revised form 30 October 1989.

SD) rats show reduced renal kallikrein synthesis and active kallikrein excretion (19,20). In this study, we examined the relationship between renal kallikrein and hemodynamic abnormalities in two STZ-D rat models: untreated SD rats and insulin-treated MD rats.

RESEARCH DESIGN AND METHODS

Protocol. Male Sprague-Dawley rats (Charles River, Wilmington, MA) weighing 220–260 g were used in all studies. Rats were housed 2–4/cage, except during 24-h urine collection, when they were housed individually in metabolic cages (Nalgene, Rochester, NY). Rats were given free access to water and standard chow at all times (24% protein, Wayne, Peoria, IL). Diabetes was induced by a single injection of STZ (65 mg/kg body wt i.v.) diluted in 0.4 ml sodium citrate buffer (0.1 M, pH 4.5). STZ was a gift from Upjohn (Kalamazoo, MI). Diabetes was confirmed by plasma glucose levels measured 24–48 h after STZ injection and subsequently at predetermined intervals throughout the study.

Two groups of diabetic rats underwent separate study. The first group (n = 11) received no insulin and displayed severe hyperglycemia (>400 mg/dl) throughout 3 wk of study (SD rats). A second group of diabetic rats (n = 18) was treated daily with 1.5–1.75 U of protamine zinc insulin (Lilly, Indianapolis, IN). Insulin was administered within 48 h after STZ administration, and plasma glucose levels were maintained in the range of 200–300 mg/dl over 5–6 wk (MD rats). Separate groups of age-matched control rats were studied with each diabetic group (n = 16 and 17, respectively).

At the end of each study, diabetic and control rats were placed individually in metabolic cages, and 24-h urine collection was obtained. Collected urine was centrifuged at low speed to remove any debris. Aliquots were stored at −20°C for measurement of glucose, active kallikrein, and prokallikrein. Immediately after completing urine collections, GFR and renal plasma flow (RPF) were measured by a single-injection method (see below). In groups of control, SD, and MD rats that were treated identically as above but did not receive radioisotopes for GFR and RPF measurements, kidneys were removed quickly under anesthesia, perfused via the renal hilus with 10 ml iced 0.9% saline, and stored at −20°C for measurement of kidney tissue active kallikrein and prokallikrein and total protein.

In a third study, the effects of treatment with a kallikrein inhibitor were studied in MD rats. Diabetes was induced and insulin given as described above. However, rats were studied after 2 wk, a period proven in preliminary studies to produce the same kallikrein and filtration changes seen at 5 wk in MD rats. Diabetic rats were treated with vehicle (n = 7) or aprotinin (n = 7), and untreated nondiabetic control rats (n = 7) were also studied. The day before measurement of GFR and RPF, 35,000 KIU aprotinin was injected subcutaneously at 0900 and 1700, and this was repeated at 0900 the day of study. During study, rats were infused intravenously with 20,000 KIU/kg aprotinin followed by 5000 KIU · kg^{-1} · min^{-1}. Aprotinin was a gift from Bayer (Wuppertal, FRG). Vehicle was 0.1 ml 0.9% saline containing 0.9% benzyl alcohol. In this study, GFR and RPF were measured by direct-clearance methods (see below). To assess the effect of aprotinin treatment on renal kallikrein activity, kallikreinlike esterase activity was measured in urine collected from the left ureter of aprotinin- and vehicle-treated diabetic rats. In these rats, kidneys were removed after GFR and RPF measurements, perfused, and stored at −20°C for measurement of kidney tissue kallikreinlike esterase activity.

GFR and RPF measurements. Measurements of GFR and RPF by the single-injection, single-sample method without urine collection were performed as previously described in detail (21). This technique was used in the initial two studies described in the protocols above. Animals were anesthetized with 80 mg/kg i.p. Inactin (Byk Gulden, Konstanz, FRG) and placed on a thermoregulated warming pad adjusted to 37°C. After 20 min on the warming pad, rats were injected via the tail vein with 5 μCi ^{51}Cr-labeled EDTA (Du Pont-NEN, Boston, MA) and 5 μCi [^{125}I]orthoiodohippuran (Amersham, Arlington Heights, IL). Heparinized blood was obtained by cardiac puncture 60 min later. Hematocrit was measured, plasma was counted for ^{51}Cr and ^{125}I, and plasma protein concentration was measured. GFR and RPF were determined from clearances of these isotopes, respectively, calculated from the plasma activity remaining at 60 min and the in vivo distribution volume of each isotope. Distribution volume of each isotope was calculated from rat body weight with algorithms derived from the study of large groups of nephrectomized control, SD, or MD rats (21).

Direct-clearance measurements of GFR and RPF were taken in the third study protocol described above. Rats were anesthetized and thermoregulated as above and prepared as follows. Tracheostomy was performed, and the left ureter was cannulated with a PE 10 cannula for urine collection. The left femoral artery was cannulated for blood sampling and direct monitoring of blood pressure via a pulse transducer. Plasma loss from surgery was replaced with isoncotic plasma (1% body wt) obtained from donor rats within the same experimental group. Plasma was infused via the tail vein over 30–40 min followed by intravenous infusion of 0.9% saline (2.8 ml/h). To measure GFR and RPF, 6 μCi ^{51}Cr-EDTA and 1.5 μCi ^{125}I-hippuran were given as intravenous boluses, followed by infusions of 10 μCi/h ^{51}Cr-EDTA and 2.5 μCi/h ^{125}I-hippuran. Both isotopes were diluted in the saline infusate such that the total fluid delivered was 2.8 ml/h. After 60 min, urine was collected for two 30-min periods in preweighed tubes kept at 4°C. Blood (200 μl) was sampled from the femoral artery at the midpoint of each urine collection for measurement of hematocrit, plasma protein concentration, and plasma radioactivity. Blood was replaced with an equal volume of plasma. Urine and plasma radioactivity were used to calculate clearances.

Kallikrein assays. Kidney tissue was prepared for assay as previously described (20). Briefly, kidneys were minced and homogenized in 5 ml phosphate-buffered saline, pH 7.4, with a Teflon/glass homogenizer. Sodium deoxycholate (0.5% final concn) was added to the homogenate, and after incubation at 4°C for 60 min, the homogenate was centrifuged (25,000 × g) at 4°C for 45 min. The resulting supernatant was used for measurement of immunoreactive kallikrein and kallikreinlike esterase activity.

Active kallikrein and prokallikrein levels in urine and kidney tissue were measured with a radioimmunoassay that incorporates a monoclonal antibody specific for active kallikrein. As described previously (20), active kallikrein was measured

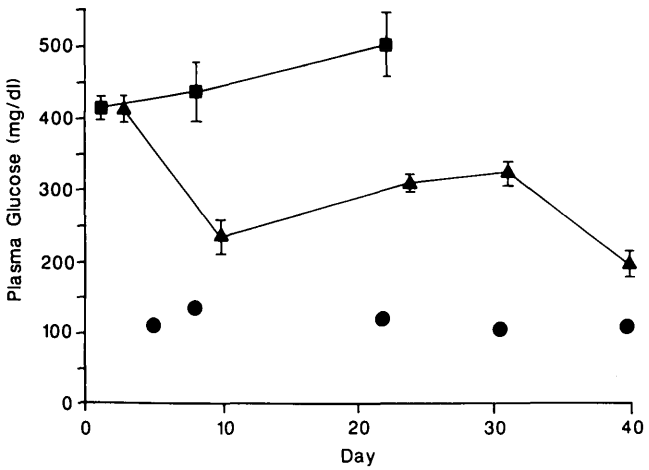

FIG. 1. Plasma glucose levels in streptozocin-induced diabetic rats not treated with insulin (severely hyperglycemic, ■), diabetic rats treated with 1.5–1.75 U/day protamine zinc insulin (moderately hyperglycemic, ▲), and control rats (●). Plasma glucose levels were measured during morning. In moderately hyperglycemic diabetic rats, first level (day 2) was obtained before insulin administration.

directly, and total kallikrein was measured in a second sample aliquot in which prokallikrein was converted to active kallikrein by prior trypsin treatment and subsequent inhibition of trypsin with soybean trypsin inhibitor. Prokallikrein concentration was derived by subtracting active kallikrein from total kallikrein. Kallikreinlike esterase activity in urine and kidney tissue homogenate was measured according to the method of Beaven et al. (22) with [^{3}H]tosylarginine methyl ester substrate.

Other assays. Plasma and urinary glucose were measured with a Glucose Analyzer 2 (Beckman, Fullerton, CA). The protein concentrations of kidney tissue homogenate and plasma were measured by the method of Lowry et al. (23) with bovine serum albumin as standard.

Statistical methods. Data are expressed as means ± SE and were analyzed by analysis of variance for single or repeated measures. The Bonferroni correction was used to guard against type I error when multiple analyses were made. Correlations were performed by linear regression analysis.

RESULTS

SD rats. Plasma glucose levels were markedly elevated the day after STZ injection (417 ± 15 mg/dl, $P < 0.001$ vs. control) and remained increased throughout the study, rising to 507 ± 45 mg/dl after 3 wk (Fig. 1). Initial body weights were similar in SD rats and their age-matched controls (213 ± 4 vs. 216 ± 2 g, respectively). However, SD rats had significantly reduced body weight after 3 wk compared with control rats (Table 1). In contrast, final kidney weight was greater in SD rats. Urine volume and urinary glucose excretion were also greatly increased in these diabetic rats (Table 1). When kidney function was measured, hematocrits were not significantly different in SD and control rats (47 ± 1 and 44 ± 1 vol/dl). Plasma protein concentration was lower in SD than in control rats (4.5 ± 0.1 vs. 5.5 ± 0.1 g/dl, $P < 0.01$).

Kidney excretion of active kallikrein, measured the day before measurement of GFR and RPF, was reduced by 30% in SD rats (Fig. 2). Active kallikrein in kidney tissue was also lower in SD compared with control rats (11.7 ± 1.9 vs. 20.5 ± 1.8 ng/mg protein, $P < 0.005$). The excretion rate of prokallikrein was slightly but significantly increased in SD compared with control rats (137 ± 9 vs. 106 ± 8 μg/24 h, $P < 0.02$). Tissue prokallikrein was not significantly different (9.2 ± 1.3 vs. 7.9 ± 0.8 ng/mg protein). Reduced renal and urinary active kallikrein were associated with reduced RPF (Fig. 2). There was a trend toward lower GFR in SD rats, but the reduction was not statistically significant. SD rats had larger kidneys, and if GFR and RPF were expressed relative to kidney weight, both were significantly reduced compared with levels in control rats.

MD rats. In these diabetic rats, plasma glucose levels before insulin treatment (day 2 after STZ administration) were similar to levels in SD rats (Fig. 1). After insulin treatment began, plasma glucose was lowered ($P < 0.001$) and maintained between 200 and 300 mg/dl throughout the study. As a result, weight gain was normal in MD rats, and both body and kidney weights were not different between MD and control rats at the time kallikrein excretion and kidney function were measured (Table 1). However, urine volume and urinary glucose excretion remained higher in MD rats than in control rats, but these levels were significantly lower than those in SD rats (Table 1). When kidney function was measured in MD rats and their controls, hematocrits were 42 ± 1 and 41 ± 1 vol/dl (NS), and plasma protein concentrations were 6.0 ± 0.2 and 6.5 ± 0.1 g/dl (NS).

In contrast to the reduction in active kallikrein excretion observed in SD rats, MD rats showed a 48% increase in kidney excretion of active kallikrein compared with weight- and age-matched control rats (Fig. 3). Prokallikrein excretion was unchanged (145 ± 15 and 120 ± 14 μg/24 h, MD and control rats, respectively). Active kallikrein and prokallikrein

TABLE 1
Characteristics of untreated severely hyperglycemic diabetic (SD) rats and insulin-treated moderately hyperglycemic diabetic (MD) rats

	Body weight (g)	Kidney weight (g)	Urine volume (ml/day)	Urine glucose (g/day)
SD	268 ± 10*	3.25 ± 0.08*	209 ± 18*	16.6 ± 1.1*
Control	373 ± 5	2.83 ± 0.05	21 ± 2	0.0040 ± 0.0001
MD	379 ± 6	2.93 ± 0.08	42 ± 4†‡	1.7 ± 0.4*‡
Control	386 ± 4	2.77 ± 0.07	27 ± 2	0.0040 ± 0.0003

Urine volume and glucose were measured the day before kidney-function studies. Body and kidney weights were measured on the day of kidney studies.
*$P < 0.001$, †$P < 0.005$, vs. respective control group.
‡$P < 0.001$ vs. SD rats.

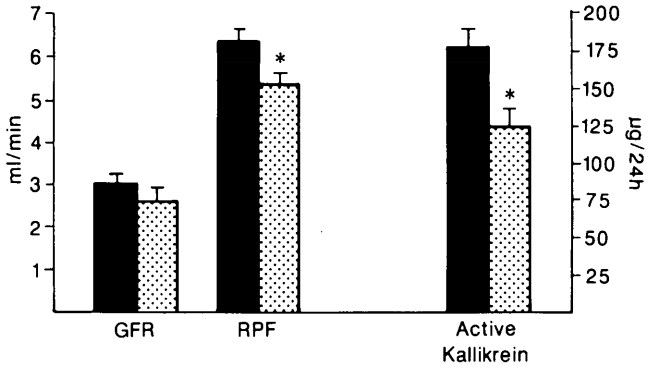

FIG. 2. Glomerular filtration rate (GFR), renal plasma flow (RPF), and renal excretion of active kallikrein in severely hyperglycemic diabetic (*dotted bars*) and control (*solid bars*) rats after 3 wk of study. Kallikrein excretion rate was measured over 24-h period immediately before measurement of GFR and RPF. *$P < 0.005$ vs. control rats.

in kidney tissue were increased in MD rats (active kallikrein, 28.4 ± 1.3 vs. 23.3. ± 1.7 ng/mg protein; prokallikrein, 23.4 ± 2.3 vs. 16.9 ± 1.8 ng/mg protein, $P < 0.05$). In association with increased tissue levels and excretion of active kallikrein, both GFR and RPF were elevated in MD rats (Fig. 3).

A subsequent study showed the same kallikrein, GFR, and RPF changes in MD rats studied 2 wk after induction of diabetes. Combining data from the three groups, kidney excretion rate of active kallikrein was directly correlated with GFR ($r = 0.44$, $P < 0.001$) and RPF ($r = 0.53$, $P < 0.001$) in SD, MD, and control rats.

Effect of kallikrein inhibitor in hyperfiltering diabetic rats. Plasma glucose levels were not different in aprotinin- and vehicle-treated MD rats (Table 2). Urine glucose excretion was also similar (2.7 ± 0.9 vs. 3.6 ± 1.0 g/day, respectively). Aprotinin treatment markedly reduced urinary kallikreinlike esterase activity (0.37 ± 0.05 vs. 2.03 ± 0.26 mU/min, $P <$ 0.005) and kidney tissue activity (81 ± 5 vs. 1101 ± 56 mU/g protein). In aprotinin-treated rats, left kidney GFR and RPF were reduced compared with function in vehicle-treated rats and as a result were not significantly different from levels in nondiabetic control rats (Table 2). Renal vascular resistance was increased by aprotinin treatment (10.1 ± 0.5 vs. 8.4 ± 0.3 mmHg · ml^{-1} · min^{-1}, aprotinin vs. vehicle, respectively; $P < 0.05$). Mean blood pressure was not different between vehicle-treated diabetic and nondiabetic control rats, and it was not changed in diabetic rats by aprotinin treatment (91 ± 7 vs. 95 ± 4 mmHg, vehicle vs. aprotinin, respectively). Hematocrits in vehicle- and aprotinin-treated diabetic rats and nondiabetic controls were 45 ± 1, 48 ± 1, and 46 ± 1 vol/dl, respectively (NS). Plasma protein concentrations were 6.1 ± 0.2, 5.9 ± 0.2, and 6.2 ± 0.2 g/dl (NS).

DISCUSSION

These studies demonstrate that STZ-SD in rats is associated with reduced kidney levels and excretion of active kallikrein, whereas STZ-D in rats in which moderate hyperglycemia is maintained by insulin treatment is associated with increased renal and urinary active kallikrein. Furthermore, these contrasts in kallikrein are associated with parallel contrasts in kidney function.

In a recent study of renal kallikrein regulation, we found that reduced active kallikrein in SD rats results from impaired prokallikrein synthesis and activation (20). Impaired prokallikrein-to-kallikrein conversion may explain why reduced active kallikrein was associated with increased prokallikrein in the urine of SD rats in this study. In studies of kallikrein regulation, we also have shown that insulin replacement increases kallikrein synthesis in SD rats, and sustained hyperinsulinemia induced by exogenous insulin raises prokallikrein synthesis above normal, together suggesting that insulin is a regulator of kallikrein in the kidney (20). Because therapeutic doses of subcutaneously administered insulin may produce hyperinsulinemia (24), it is possible that insulin treatment contributed to the increase in renal and urinary kallikrein we observed in MD rats in this study. Whatever the cause, the rapid rate at which kallikrein turns over in the kidney strongly suggests that a sustained increase in excretion rate could not occur without increased kidney synthesis of kallikrein (25).

The contrast in kidney function we observed in SD and MD rats has been reported previously. Hostetter et al. (2) demonstrated that untreated STZ-SD rats have increased glomerular arteriolar resistance and reduced glomerular plasma flow, filtration pressure, and single-nephron GFR. We also observed reduced RPF in this model, but GFR was not significantly reduced in our study. This may be because plasma protein concentration was reduced in SD rats. This reduction in oncotic pressure would favor filtration and tend to offset reduced RPF. In Hostetter et al., insulin-treated MD rats showed reduced glomerular arteriolar resistance and increased glomerular plasma flow, filtration pressure, and single-nephron GFR. We also found increased GFR and RPF in this model by two different methods.

Our data, together with other findings, suggest that changes in kallikrein or the kinin produced by it may contribute to the renal hemodynamic differences in these diabetic models. Kinins dilate glomerular arterioles when infused into the rat kidney or when applied to the luminal or antiluminal side of isolated perfused glomerular arterioles (11,26). This action may be direct or may be mediated by eicosanoids, because bradykinin stimulates PGE_2 and 6-keto-$PGF_{1\alpha}$ production by isolated canine afferent arterioles (14). Eicosanoid production is also stimulated in cultured rat

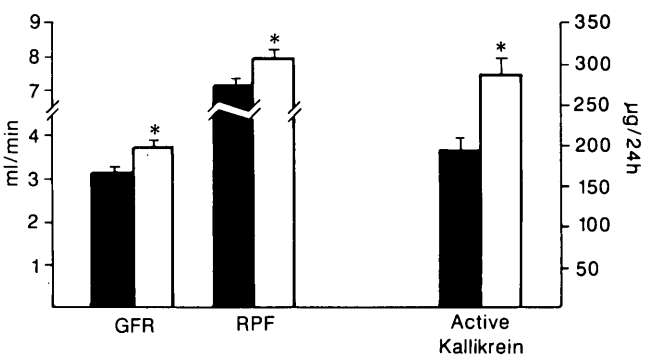

FIG. 3. Glomerular filtration rate (GFR), renal plasma flow (RPF), and renal excretion of active kallikrein in moderately hyperglycemic diabetic (*open bars*) and control (*solid bars*) rats after 5–6 wk. Kallikrein excretion was measured over 24-h period immediately before measurement of GFR and RPF. *$P < 0.005$ vs. control rats.

TABLE 2
Effects of kallikrein inhibitor aprotinin on left kidney function in hyperfiltering moderately hyperglycemic diabetic (MD) rats

	Body weight (g)	Plasma glucose (mg/dl)	Urine volume (μl/min)	Glomerular filtration rate (ml/min)	Renal plasma flow (ml/min)
MD					
Vehicle treated	336 ± 9	314 ± 42	17.5 ± 3.7	2.01 ± 0.10	5.95 ± 0.32
Aprotinin treated	331 ± 8	392 ± 34	13.4 ± 3.6	1.59 ± 0.05*	4.98 ± 0.28†
Nondiabetic control	364 ± 11	119 ± 4‡	14.3 ± 3.4	1.59 ± 0.13†	4.51 ± 0.36†

Plasma glucose and urine volume were measured when left kidney function was measured.
*$P < 0.02$, †$P < 0.05$, vs. vehicle.
‡$P < 0.001$ vs. either diabetic group.

glomerular mesangial cells by addition of bradykinin, the kinin produced by rat renal kallikrein, or lysylbradykinin, the kinin produced by human renal kallikrein (13).

The demonstration of such effects of applied kinins is given physiological relevance by the recent localization of kallikrein within connecting tubule cells that are anatomically close to the glomerulus. The connecting tubule segment of the distal tubule forms a second loop after the macula densa, passing adjacent to the afferent arteriole (10). Careful immunocytochemical studies in rat and human kidney reveal that kallikrein-containing connecting tubule cells are within a few microns of the afferent arteriole in >80% of nephrons (10,27). In addition, kininogen substrate is produced in the principal cells that are in the same nephron segment (28). Therefore, it is plausible that kinins are generated in the region of the afferent arteriole. In an initial histochemical study in SD rats, we found that kallikrein is markedly reduced in connecting tubule cells (unpublished observations).

Although a highly significant correlation existed between active kallikrein excretion and GFR and RPF in this study, correlation coefficients suggest that only 20–30% of the changes in function can be attributed to a change in kallikrein. This raises at least two possibilities. First, kallikrein excretion rate may not accurately reflect intrarenal kinin production. If the actions of kallikrein on renal hemodyanmics are mediated through kinins, we may have found a closer correlation between urinary kinins and function. Second, other endocrine or paracrine factors probably contribute to hemodynamic changes in diabetes. There is evidence that changes in vasoactive prostaglandins and thromboxane contribute to vasodilation or vasoconstriction in the models we studied (9), and the renin-angiotensin system may contribute to raised filtration pressure in the MD rat (4). Considerable data link the regulation and action of these latter systems with the kallikrein-kinin system, and it is plausible that all three, and other factors, interact to produce hemodynamic changes in diabetes.

The relationship between kallikrein activity and hemodynamic abnormalities in diabetes is further supported by our finding that aprotinin treatment reduced GFR and RPF in hyperfiltering MD rats. Although aprotinin is not specific as an inhibitor of kallikrein, other serine proteases known to be inhibited by aprotinin do not have a recognized effect on kidney function, suggesting that the effects we observed are most likely due to kallikrein inhibition. In other states in which kallikrein production is stimulated, aprotinin has also been observed to lower GFR and RPF (29,30). Although an effect of aprotinin on RPF or GFR in nondiabetic rats has not always been observed (29), we found in preliminary studies that the present dose lowered function in control rats. This suggests that kallikrein and kinins may have the same regulatory influence on renal hemodynamics in nondiabetic rats as in diabetic rats, but their actions may be accentuated in diabetes. This would be consistent with the notion that the kallikrein-kinin system has a role in physiological regulation of the glomerular circulation, possibly as a modulator of tubuloglomerular feedback (12).

Finally, we recently discovered that dietary protein restriction reduces renal kallikrein synthesis and excretion in nondiabetic rats in parallel with a fall in GFR and RPF, and a high-protein diet raises renal kallikrein excretion, GFR, and RPF in nondiabetic and SD rats (31,32). These findings provide a further link between changes in renal kallikrein and renal hemodynamics and raise the possibility that the reduction in GFR and RPF in hyperfiltering diabetic rats after protein restriction may be mediated in part by reduced renal kallikrein activity (3). The role of kallikrein and kinins in regulating glomerular function can now be further assessed at a microcirculation level with newly available kinin-receptor antagonists (33).

ACKNOWLEDGMENTS

This study was supported by National Institutes of Health Grant DK-35977 and Merit Review funding from the Veterans Administration. J.N.H. was supported by a Clinical Postdoctoral Fellowship Award from the Medical University of South Carolina, College of Graduate Studies.

We acknowledge the technical assistance of Amy Frayser and Michael Bigelow in these studies. We also thank Debra Riebe for assistance in preparing the manuscript.

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