Kinin, a Mediator of Diabetes-Induced Glomerular Hyperfiltration

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Renal kallikrein is increased in diabetic patients and streptozotocin (STZ)-induced diabetic rats with hyperfiltration. Chronic inhibition of renal kallikrein reduces glomerular filtration rate (GFR) and renal plasma flow (RPF) in hyperfiltering STZ-induced diabetic rats. To investigate whether these actions of kallikrein and its inhibition are kinin-mediated, we used a B_2-kinin receptor antagonist (BKA). In STZ-induced diabetic rats with hyperfiltration, renal kallikrein excretion rate was significantly increased ($P \leq 0.01$), and kinin excretion rate was increased 57%, as compared with control rats. Left kidney GFR and RPF were measured before and during a 40-min infusion of BKA (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or vehicle. Infusion of the kinin receptor antagonist reduced the GFR and RPF significantly. GFR was reduced by 18%, from an average baseline value of 2.07 ± 0.11 to 1.70 ± 0.06 ml/min, $P \leq 0.001$ (means ± SE). RPF was reduced by 25%, from 6.74 ± 0.38 to 5.06 ± 0.17 ml/min, $P \leq 0.001$. Total renal vascular resistance was significantly increased during BKA infusion, $P \leq 0.001$. Vehicle infusion for the same period had no significant effect on GFR, RPF, or renal vascular resistance. These findings further support the hypothesis that increased renal production of kinins contributes to the renal vasodilation of diabetes. ***Diabetes*** **44:156–160, 1995**

Abnormalities in glomerular hemodynamics have been observed in patients having type I diabetes, as well as in early stages of experimental diabetes (1–3). Micropuncture studies in diabetic rats have shown that hyperfiltration occurs as a consequence of reduced glomerular arteriolar resistance, resulting in increases in glomerular plasma flow and capillary hydraulic pressure (2). These early hemodynamic disturbances have been suggested to contribute to the initiation and progression of diabetic glomerulopathy (4). The mechanism(s) responsible for these hemodynamic abnormalities is undetermined. Numerous mediators of hyperfiltration have been proposed, but as yet no single candidate has been proven to be responsible.

We have accumulated data that support a role for the renal kallikrein-kinin system as a mediator of diabetes-induced hyperfiltration. In diabetic rats treated with enough insulin to produce a state of moderate hyperglycemia, renal tissue and urinary active kallikrein levels increased, and this increase in kallikrein activity is associated with reduced renal vascular resistance and increased glomerular filtration rate (GFR) and renal plasma flow (RPF) (5). Chronic treatment of these hyperfiltering diabetic rats with aprotinin, a kallikrein inhibitor, reduced GFR and RPF to levels that were not different from those of controls (5). Renal active kallikrein excretion rate is also increased in type I diabetic patients who have glomerular hyperfiltration (6).

Although aprotinin reversed the hyperfiltration and hyperperfusion induced by diabetes, its effects on renal function could be due to direct inhibition of renal kallikrein and, consequently, the release of kinins or, because of its polycationic nature, the effects are nonspecific. Therefore, this study was undertaken to clarify the role of kinins as mediators of glomerular hyperfiltration in diabetes. We studied hyperfiltering diabetic rats treated with a specific B_2-kinin receptor antagonist (BKA).

RESEARCH DESIGN AND METHODS

Induction of diabetes. Male Sprague-Dawley rats (Charles River, Wilmington, MA) weighing 200–220 g were used in all studies. Rats were housed two or three per cage in a light- and temperature-controlled room and had free access to food and water. Diabetes was induced by a single intravenous injection of streptozotocin (STZ) (65 mg/kg body wt). The STZ was a gift from Upjohn (Kalamazoo, MI). Diabetes was confirmed by plasma glucose levels, measured 24 h after STZ injection and subsequently at predetermined intervals throughout the study. One day after induction of diabetes, the diabetic rats were treated daily with 1.5–1.75 U of protamine zinc insulin (Lilly, Indianapolis, IN). Plasma glucose levels were maintained in the moderate-to-hyperglycemic range (250–350 mg/dl) over 2–3 weeks. Nondiabetic control rats were injected with vehicle.

Protocol. To study renal function, rats were anesthetized with an intraperitoneal injection of Inactin, 100 mg/kg body wt (BKY Gulden, Konstanz, Germany). They were placed on a thermoregulated heating pad, and rectal temperature was maintained at 36–37°C throughout the experiment. A tracheostomy was performed, and the left ureter was cannulated with polyethylene 10 tubing for collection of urine. The left femoral artery and vein were cannulated with polyethylene 50 tubing for blood sampling, direct recording of blood pressure, and infusion of agents. Blood loss from surgery (1% body wt) was replaced over 20–30 min with plasma from donor rats. After completion of surgery, rats were allowed to recover for 60 min before renal function was measured. Saline (0.9%) was infused at 2.0 ml/h during the recovery period.

To study the effects of kinin receptor blockade on renal hemodynamics, GFR and RPF were measured during baseline and subsequently during infusion of a BKA (D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-DPhe-Thi-Arg-trifluoroacetic acid). The antagonist was given as an intravenous bolus of 10 $\mu g/kg$, followed by an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 40 min. A second group of diabetic rats was infused with vehicle (0.9% saline) throughout the experimental period and provided time-control data. The effects of kinin antagonist on renal function in nondiabetic control rats were also studied.

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GFR, glomerular filtration rate; RPF, renal plasma flow; BKA, B_2-kinin receptor antagonist; STZ, streptozotocin; TRVR, total renal vascular resistance; CEI, converting enzyme inhibitor; ANP, atrial natriuretic peptide.

TABLE 1
Body weight, left kidney weight, plasma glucose, mean blood pressure, hematocrit, and filtration fraction in control and moderately diabetic rats

	n	Body wt (g)	Left kidney wt (g)	Plasma glucose (mg/dl)	Mean blood pressure (mmHg)	Hematocrit (%)	Filtration fraction
Control rats	12	377 ± 8	1.50 ± 0.05	123 ± 3	104 ± 2	48 ± 1	0.32 ± 0.01
Moderately diabetic rats	13	368 ± 8	1.76 ± 0.08*	283 ± 33†	105 ± 3	47 ± 1	0.33 ± 0.02

Data are means ± SE. n = number of animals in each group. * $P < 0.01$ vs. C; † $P < 0.002$ vs. C.

Clearance measurements. GFR and RPF were measured by the renal clearance of ^{51}Cr-labeled EDTA (Du Pont-NEN, Boston, MA) and ^{125}I-labeled Orthoiodohippurate (Amersham, Arlington Heights, IL), respectively. An intravenous bolus of 2 μCi/100 g body wt ^{51}Cr-EDTA and 0.5 μCi/100 g body wt ^{125}I-labeled Hippuran in 150 μl saline was followed by infusion of 10 μCi/h ^{51}Cr-EDTA and 2.5 μCi/h ^{125}I-Hippuran. These isotopes were mixed with the saline or the kinin antagonist, such that total fluid infused remained at 2.0 ml/h. Infusion of isotopes began 60 min before clearance measurements. Urine was collected from the left ureter into preweighted polypropylene tubes during consecutive 20-min periods and kept on ice to preserve kinins and kallikrein. Arterial blood (200 μl) was drawn at the midpoint of each collection for measurement of hematocrit and radioactivities of ^{51}Cr and ^{125}I. Blood drawn was replaced with an equal volume of rat plasma. Radioactivities in urine and plasma were counted in a dual channel γ-counter, and clearances are expressed as ml/min. Hippuran extraction was determined from concentrations in peripheral arterial blood and renal venous blood drawn at the end of each study. RPF was corrected for the extraction ratio. In preliminary studies, we determined that the kinin antagonist did not alter Hippuran extraction. Total renal vascular resistance (TRVR) was calculated by the following formula: TRVR equals mean blood pressure (mmHg) divided by the renal blood flow. Renal blood flow equals RPF/1 minus hematocrit.

Assays. Urinary active kallikrein and prokallikrein were measured by a monoclonal antibody radioimmunoassay that has been described in detail (5). Prokallikrein was determined by assaying active kallikrein in each sample before and after trypsin treatment, which converts all prokallikrein to active kallikrein, and subtracting the pretreatment concentration from the total after trypsin. To measure urinary kinins, urine was collected directly from the ureter into iced tubes. One volume of urine, which was free of blood as determined with Labstix (Miles, Elkhart, IN), was placed in 4 vol of absolute ethanol. The mixture was centrifuged at 5,000*g*, and the supernatant was recovered and air-dried. The dried residue was reconstituted in kinin assay buffer for direct radioimmunoassay measurement (7). Plasma glucose levels were measured with a Glucose Analyzer II (Beckman, Fullerton, CA).

Statistical analysis. Data are expressed means ± SE and were analyzed by analysis of variance for repeated measurements. Differences were considered to be significant if $P \leq 0.05$. In analyzing data from renal function studies, Scheffe's contrast test was used to take advantage of preassigned baseline and kinin antagonist infusion periods. This test guards against type I diabetes as a result of multiple analyses.

RESULTS

Characteristics of the diabetic state. Despite similar body weight gains between control and insulin-treated, moderately diabetic rats, left kidney weight was significantly increased by 17% in moderately diabetic rats compared with control rats ($P \leq 0.02$) (Table 1). Plasma glucose level was significantly elevated in the diabetic group, compared with controls (293 ± 33 vs. 123 ± 3 mg/dl, moderately diabetic vs. control rats, respectively, $P \leq 0.001$), but was maintained within the moderately hyperglycemic range with insulin treatment. There was no difference in mean blood pressure or hematocrit between control and moderately diabetic rats (Table 1).

Effects of moderate hyperglycemia on renal hemodynamics. Figure 1 shows the renal clearance measurements in control and moderately diabetic rats. In moderately diabetic rats, GFR and RPF increased 24 and 20%, respectively, compared with control rats (GFR, 2.05 ± 0.08 vs. 1.65 ± 0.08 ml/min; RPF, 6.23 ± 0.32 vs. 5.21 ± 0.26 ml/min; moderately diabetic vs. control, respectively, $P \leq 0.05$). The filtration fraction was unchanged (0.33 ± 0.02 vs. 0.32 ± 0.01, moderately diabetic vs. control, respectively). TRVR was significantly reduced in moderately diabetic rats compared with control rats (7.44 ± 0.52 vs. 8.81 ± 0.24 mmHg · ml^{-1} · min^{-1}, moderately diabetic vs. control, respectively, $P \leq 0.05$) (Fig. 1).

Kallikrein and kinin excretion rates. Figure 2 shows the total, active, and prokallikrein urinary excretion rates in control and moderately diabetic rats. Total and prokallikrein urinary excretion increased 40 and 123%, respectively, in moderately diabetic compared with control rats (total, 177 ± 11 vs. 127 ± 12 ng/min; prokallikrein, 67 ± 10 vs. 30 ± 4 ng/min; moderately diabetic vs. control, respectively, $P \leq 0.01$). Active kallikrein tended to increase, but was not significantly increased (108 ± 6 vs. 97 ± 9 ng/min, moderately diabetic vs. control, respectively, $P \leq 0.05$). The kinin receptor antagonist had no significant effect on the total, active, and prokallikrein excretion rates.

The urinary excretion rate of kinins in control and moderately diabetic rats is shown in Fig. 3. There was a 57% increase in kinin excretion in the diabetic group compared with control rats (57.7 ± 13 vs. 36.7 ± 7 pg · min^{-1} · kg^{-1} body wt, moderately diabetic vs. control, respectively). This increase in kinins did not reach statistical significance.

Effects of kinin receptor blockade on moderate diabetes–induced changes in renal function. Table 2 shows the

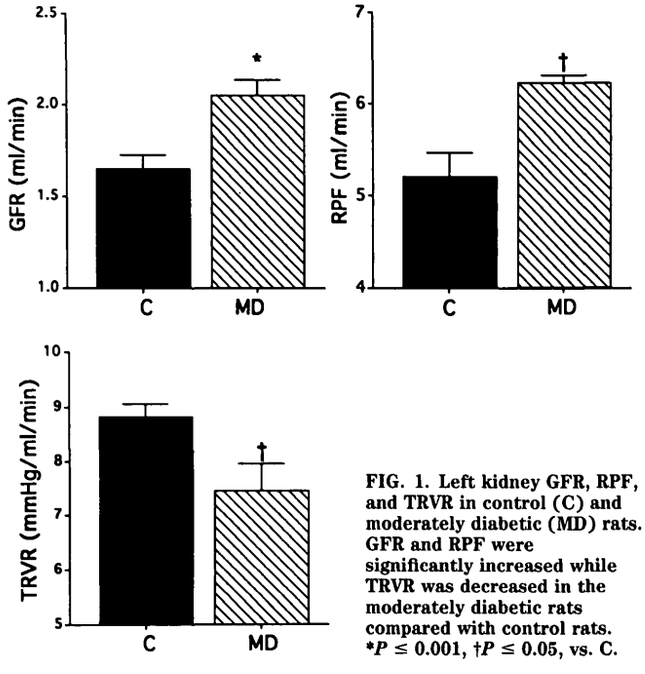

FIG. 1. Left kidney GFR, RPF, and TRVR in control (C) and moderately diabetic (MD) rats. GFR and RPF were significantly increased while TRVR was decreased in the moderately diabetic rats compared with control rats. *$P \leq 0.001$, †$P \leq 0.05$, vs. C.

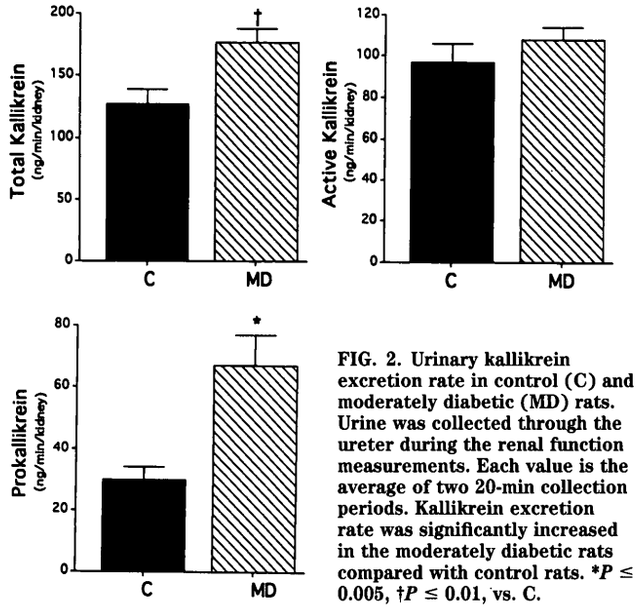

FIG. 2. Urinary kallikrein excretion rate in control (C) and moderately diabetic (MD) rats. Urine was collected through the ureter during the renal function measurements. Each value is the average of two 20-min collection periods. Kallikrein excretion rate was significantly increased in the moderately diabetic rats compared with control rats. *$P \leq 0.005$, †$P \leq 0.01$, vs. C.

body weight, left kidney weight, and plasma glucose levels in moderately diabetic rats infused with vehicle (moderately diabetic + vehicle) or the kinin receptor antagonist (moderately diabetic + BKA). There was no significant difference in any of these parameters between the two groups.

Mean arterial pressure, hematocrit, urine volume, and filtration fraction were not different during baseline measurements between the two diabetic groups, and these parameters did not change significantly during infusion of either the kinin antagonist or vehicle (Fig. 4).

Figure 5 shows the left kidney GFR, RPF, and TRVR in moderately diabetic rats treated with vehicle or the kinin receptor antagonist. Baseline GFR and RPF were not different between the two diabetic groups but were significantly higher than those in normal control rats (cf Fig. 1). Infusion of the kinin receptor antagonist for 40 min significantly

TABLE 2
Body weight, left kidney weight, and plasma glucose levels in moderately diabetic rats treated with vehicle and moderately diabetic rats treated with BKA

	n	Body wt (g)	Left kidney wt (g)	Plasma glucose (mg/dl)
Moderately diabetic rats + vehicle	11	356 ± 8	1.69 ± 0.05	314 ± 37
Moderately diabetic rats + BKA	7	353 ± 7	1.58 ± 0.06	325 ± 28

Data are means ± SE. n = number of animals in each group.

reduced the GFR and RPF and increased the TRVR. GFR was reduced by 18%, from an average baseline value of 2.07 ± 0.11 ml/min to an average experimental value of 1.70 ± 0.06 ml/min ($P \leq 0.001$). RPF was reduced by 25%, from an average baseline value of 6.74 ± 0.38 ml/min to an average experimental value of 5.06 ± 0.17 ml/min ($P \leq 0.001$). TRVR was increased by 31%, from an average baseline value of 7.69 ± 0.66 mmHg · ml^{-1} · min^{-1} to an average experimental value of 11.28 ± 0.65 mmHg · ml^{-1} · min^{-1} ($P \leq 0.001$).

Vehicle (0.9% saline) infusion for a period of 40 min had no significant effect on left kidney GFR, RPF, and TRVR (Fig. 5). The average baseline values of GFR (2.05 ± 0.12 ml/min) and RPF (6.64 ± 0.30 ml/min) were not significantly different from experimental values (GFR, 2.18 ± 0.15 ml/min and RPF, 6.42 ± 0.22 ml/min). TRVR also remained unchanged during vehicle infusion (7.36 ± 0.38 vs. 7.83 ± 0.38 mmHg · ml^{-1} · min^{-1}, baseline vs. experimental, respectively).

Shown in Table 3 are the effects of infusing the kinin receptor antagonist in nondiabetic control rats (n = 5). Infusion of 0.5 μg · kg^{-1} · min^{-1} of the kinin antagonist had no effect on mean blood pressure, hematocrit, urine volume, or filtration fraction. The GFR tended to show an increase after antagonist, but this was not significant. There were also no changes in RPF or TRVR.

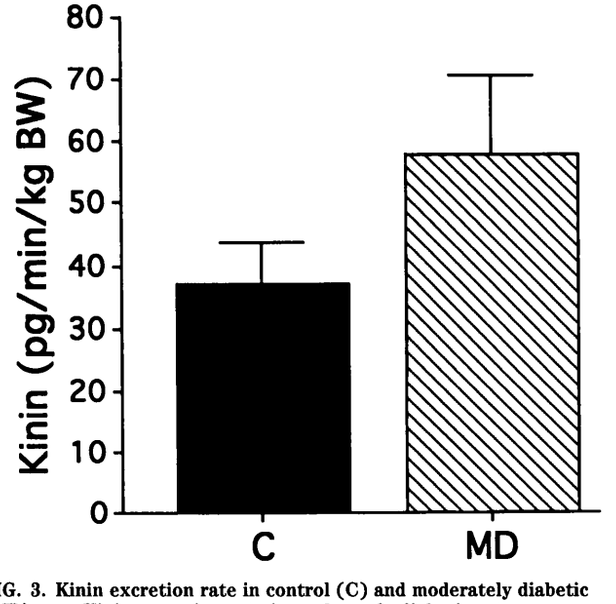

FIG. 3. Kinin excretion rate in control (C) and moderately diabetic (MD) rats. Kinin excretion rate in moderately diabetic rats was increased by 57% compared with that in control rats.

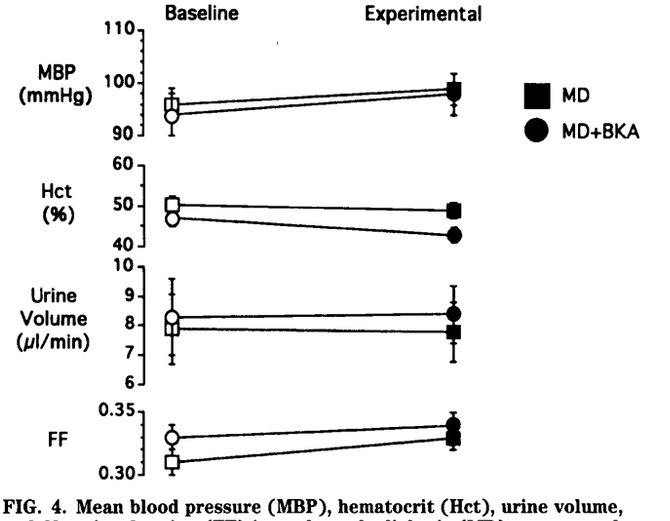

FIG. 4. Mean blood pressure (MBP), hematocrit (Hct), urine volume, and filtration fraction (FF) in moderately diabetic (MD) rats treated with vehicle throughout the study period (baseline and experimental) and moderately diabetic rats treated with vehicle during the baseline period, followed by infusion of the kinin receptor antagonist (MD + BKA) during the experimental period. Each point is the mean of two 20-min collection periods. No significant difference was observed between the baseline and experimental values in any of the parameters.

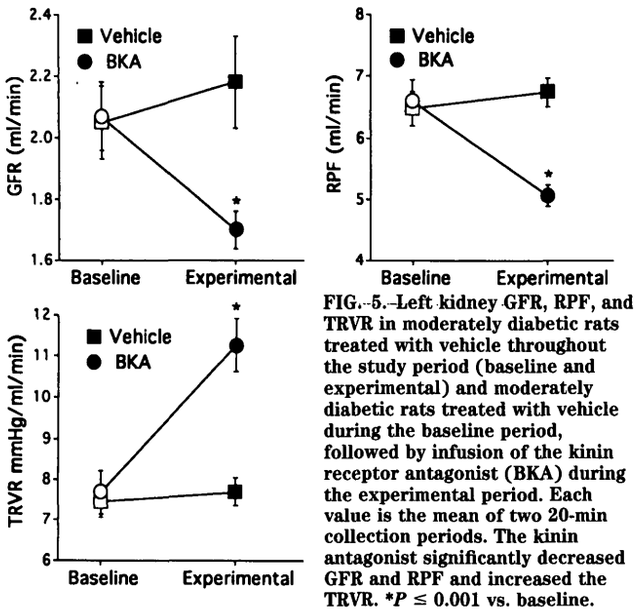

FIG. 5.—Left kidney GFR, RPF, and TRVR in moderately diabetic rats treated with vehicle throughout the study period (baseline and experimental) and moderately diabetic rats treated with vehicle during the baseline period, followed by infusion of the kinin receptor antagonist (BKA) during the experimental period. Each value is the mean of two 20-min collection periods. The kinin antagonist significantly decreased GFR and RPF and increased the TRVR. *$P \leq 0.001$ vs. baseline.

DISCUSSION

These data demonstrate that acute treatment of hyperfiltering diabetic rats with a kinin receptor antagonist reduced the elevated GFR and RPF and reversed the reduced renal vascular resistance to control values. This response is in contrast with that of normal rats, in which the kinin antagonist produced no significant change in any of these parameters. The data also support our earlier finding that aprotinin, a kallikrein inhibitor that blocks the generation of kinins, reduced the hyperfiltration and hyperperfusion of these diabetic rats. Taken together, these findings strongly implicate the kallikrein-kinin system in mediating the hyperfiltration state in diabetes.

The contribution of glomerular hemodynamic abnormalities, rather than metabolic factors, to the progression of diabetic nephropathy is supported by the observation that increases in intraglomerular capillary pressure accelerates the development of glomerular injury, which eventually leads to glomerulosclerosis (4,8). Treatment of hyperfiltering diabetic rats with converting enzyme inhibitors (CEIs) reduces the elevated capillary pressure and limits mesangial expansion and glomerular basement membrane thickening (9). However, in these studies, GFR and RPF remained elevated after CEI treatment, which suggests that although angiotensin II sustains the raised intraglomerular pressure, other factors may principally cause the increases in RPF and GFR in diabetes.

TABLE 3
Mean blood pressure, hematocrit, urine volume, filtration fraction, GFR, RPF, and TRVR in nondiabetic control rats treated with vehicle (baseline period) followed by infusion of BKA (experimental period)

	Baseline	Experimental
Mean blood pressure (mmHg)	101 ± 2	104 ± 5
Hematocrit (%)	51 ± 1	50 ± 1
Urine volume ($\mu l \cdot min^{-1} \cdot kidney^{-1}$)	9 ± 6	10 ± 7
Filtration fraction	0.28 ± 0.01	0.30 ± 0.01
GFR (ml/min)	1.62 ± 0.1	1.99 ± 0.20
RPF (ml/min)	5.74 ± 0.31	6.54 ± 0.51
TRVR ($mmHg \cdot ml^{-1} \cdot min^{-1}$)	8.81 ± 0.24	8.08 ± 0.43

Data are means ± SE. Each point is the mean of two 20-min collection periods.

Numerous renal vasodilators have been examined as mediators of hyperfiltration in diabetes. Studies of prostaglandins have yielded conflicting results. Synthesis of prostaglandins was shown to be either increased or unchanged in glomeruli of hyperfiltering diabetic rats (10–12). Furthermore, treatment of these hyperfiltering diabetic rats with cyclooxygenase or thromboxane inhibitors in some cases reduced and in others had no effect on the elevated GFR and RPF (12,13). A role for the renin angiotensin system as a mediator of hyperfiltration in diabetes has received considerable attention. Diabetic rats with hyperfiltration show either an increase or no change in plasma renin activity, renal renin activity, or renal renin mRNA levels (14–17). Treatment of diabetic rats with losartan, an angiotensin II receptor blocker, reduced the glomerular capillary pressure without affecting the raised GFR and RPF, thereby suggesting that raised intrarenal renin activity contributes to the glomerular hypertension of diabetes (18). Atrial natriuretic peptide (ANP) is increased in the plasma of diabetic rats, and treatment of these rats with antisera directed against ANP reversed the hyperfiltration to normal values (19). Evidence has also emerged suggesting that nitric oxide plays a role in the renal hyperfiltration of diabetes (20,21). Relevant to this finding and our data, kinins are potent stimulators of nitric oxide synthesis (22).

Although kinin excretion rate was not significantly elevated in the diabetic rats we studied, a strong trend was observed. Note that measurement of kinins in ureteral samples may not accurately reflect intrarenal production. Measurement of interstitial kinin levels, as we have recently begun to do, is likely to be more relevant to hemodynamic actions of kinins in the kidney (23). Along the same line, we also did not find increased active kallikrein in ureteral urine of diabetic rats, although total and prokallikrein urinary excretions were increased. In a previous study, we did find an increase in active kallikrein excretion rate measured over 24 h, as well as an increase in renal tissue levels (5). Although we cannot explain with certainty the reason for the differences in kallikrein excretion between these studies, several relevant points can be made. In this study, kallikrein was measured in urine collected directly from the ureter over a much shorter interval. A shorter collection period may have prevented us from seeing an increase. The difference in the method of urine collection also could have resulted in the discrepancy. Although in vitro activation of urinary prokallikrein collected over a prolonged period could explain this difference, we have previously excluded this phenomenon as contributing to increased urinary active kallikrein (our unpublished observations). The most important point to be made is that urinary or even tissue measurements of any of these components of the kallikrein-kinin system do not give as clear a picture of system involvement as does the response to antagonists. The demonstration that acute treatment of these hyperfiltering rats with a selective BKA reduces GFR and RPF lends the strongest support to the hypothesis that kinins contribute to the altered glomerular hemodynamics of diabetes.

If kinins generated in the kidney regulate glomerular hemodynamics, several recent findings provide anatomical and functional frameworks for the mechanisms by which the renal kallikrein-kinin system regulates glomerular hemody-

namics. Immunocytochemical studies in the rat and human kidney demonstrate that kallikrein is localized in the connecting tubule cells, a nephron segment that passes within 3 μm of the afferent arteriole (24,25); the low molecular weight kininogen substrate resides in the principal cells, which are adjacent to the kallikrein-containing cells (26), thus allowing generation of kinins in the interstitium near the afferent arteriole. This is supported by recent localization and quantitation of kinins in interstitial fluid (23). Finally, B_2-kinin receptors have been demonstrated in isolated glomerular membranes, and antiluminal addition of kinins to isolated afferent arterioles reduces resistance (27,28).

With these structure-function relationships in mind, the findings of this study provide support for the hypothesis that increased renal production of kinins contributes to renal vasodilation of diabetes and suggest that kinin receptor blockade is another intervention that could help to define the contributions of altered hemodynamics to diabetic nephropathy.

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