# Acute and chronic responses of human renal kallikrein and kinins to dietary protein

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BOLIN, PAUL, AYAD A. JAFFA, PHILIP F. RUST, AND RONALD K. MAYFIELD. *Acute and chronic responses of human renal kallikrein and kinins to dietary protein.* Am. J. Physiol. 257 (Renal Fluid Electrolyte Physiol. 26): F718–F723, 1989.—Glomerular filtration rate (GFR; creatinine clearance) and renal excretion rates of active kallikrein, prokallikrein, and kinins were measured in seven normal male subjects after a week on a constant low (40 g/day)-protein diet (LP) and during a subsequent week when only protein content was increased to 140 g/day (HP). Renal kinin excretion increased from 19.7 ± 1.2 μg/day on *day 7* of LP to 26.0 ± 2.5 on *day 1* of HP ($P < 0.002$), and this higher rate persisted during HP. Active kallikrein excretion increased from 105 ± 16 to 171 ± 40 μg/day on *day 2* of HP ($P < 0.006$). Prokallikrein excretion did not increase significantly until *day 4* of HP, 52 ± 16 vs. 96 ± 38 μg/day ($P < 0.03$). The increases in active kallikrein and kinin excretion preceded an increase in GFR, which went from 117 ± 6.8 ml/min on LP to 130 ± 10 ml/min on *day 5* of HP ($P < 0.003$). At the end of the LP diet, acute ingestion of 40 g of a casein solution produced an increase in kinin excretion after 2 h (586 ± 64 vs. 402 ± 33 pg/min, $P < 0.001$) and further to 640 ± 74 pg/min at 3 h ($P < 0.001$). This was accompanied by an increase in GFR at 3 h (154 ± 18 vs. 132 ± 10 ml/min, $P < 0.05$). Kinin excretion rate correlated directly with GFR during both chronic ($r = 0.87$) and acute ($r = 0.77$) studies. The data suggest that increased renal kallikrein activity and kinin production may contribute to renal vasodilation and the rise in renal perfusion and filtration produced by dietary protein.

glomerular filtration; kallikrein-kinin system; nutrition

VEGETARIANS HAVE LOWER glomerular filtration rates (GFR) than omnivorous subjects, and controlled studies show that GFR increases when dietary protein intake increases (4, 22, 33). An increase in filtration can be observed in humans acutely after ingestion of protein or ingestion or intravenous infusion of amino acids (4, 6, 9, 14, 24, 31, 33). The rise in GFR is primarily due to increased renal plasma flow (RPF), resulting from a fall in renal vascular resistance (6, 14, 24, 31, 33). Moreover, studies in experimental animals fed high protein or infused with amino acids show that glomerular arteriolar resistance falls (16, 21).

Studies in humans to identify the mediators of protein-induced renal vasodilation have examined the possible roles of several endocrine and paracrine factors. Although the combined effects of insulin, glucagon, and growth hormone may play some role, it appears that none of these hormones is independently responsible (5). Measurement of atrial natriuretic peptide (ANP) levels after oral protein loading suggests that this vasodilator is not involved (7). Plasma renin activity increases during chronic high protein feeding (23), yet the effects of converting enzyme inhibitor on protein-induced filtration changes are not consistent (11, 19). In any case, renal vasodilation cannot be explained by increased angiotensin II (ANG II) levels. Urinary excretion of eicosanoids have not shown consistent changes after meat ingestion or amino acid infusion (14, 19, 24), but indomethacin pretreatment can attenuate acute GFR and RPF responses to protein (24).

Several recent studies suggest that renal kallikrein and the kinins generated by it may participate in regulating GFR. In human and rat kidney, histochemical studies demonstrate that the afferent arteriole of nearly all nephrons is adjacent to connecting tubule cells containing kallikrein (1, 34). Kinins stimulate eicosanoid production by isolated afferent arterioles and cultured mesangial cells, and both kallikrein and kinins release renin from isolated intact glomeruli (2, 3, 15, 32). Finally, studies of kallikrein and kininase inhibitors suggest that kallikrein and kinins may modulate tubuloglomerular feedback (26). We recently discovered that renal kallikrein synthesis and excretion in rats is altered by the level of protein intake, and in rats fed high protein, GFR and RPF are lowered by treatment with a kallikrein inhibitor (16a). In the present human studies we examined the acute effects of an oral protein load and the effects of a chronic change in protein intake on renal excretion of active kallikrein, prokallikrein, and kinins.

## METHODS

*Subjects.* Seven Caucasian males were studied in the General Clinical Research Center of the Medical University of South Carolina Hospital. The protocol was approved by the Institutional Review Committee for Human Research, and informed consent was obtained from all subjects. The subjects ranged in age from 22 to 32 yr and were within 20% of ideal weight. None was taking medications nor had any illnesses. Renal function was normal in all subjects, as assessed by creatinine clearance, urinary protein excretion, and urinalysis. Complete blood count and routine serum chemistries showed no significant abnormalities.

*Clinical protocol.* During the first 7 days, all subjects consumed a mixed diet containing 2,400 kcal, 40 g pro-

tein, 380 g carbohydrate, 80 g fat, 150 meq sodium, 80 meq potassium, 800 mg calcium, and 2 g phosphorous. During the subsequent 7 days, the protein intake of the mixed diet was increased to 140 g. On the 40-g diet, animal-source protein contributed 9 g and vegetable protein 31 g. During the second week, animal protein was increased to 109 g and vegetable protein was unchanged. This was offset by a reduction in carbohydrate to 280 g, and calorie, electrolyte, and mineral content were unchanged.

On the last 2 days of the low-protein diet and throughout the high-protein diet, urine was collected each 24 h for measurements of sodium, potassium, creatinine, osmolality, active kallikrein, prokallikrein, and kinins. Urinary total protein, urea, and aldosterone excretion were measured on the last 2 days of each diet period. Immediately after each voiding, urine was divided into equal 24-h aliquots. One aliquot was collected with concentrated HCl (final pH <2) and pepstatin (0.2 mg/24-h collection) to preserve kinins and prevent further kinin generation (28). Urine preserved for kinins was frozen at −20°C until assayed. Urine for kallikrein, taken from the second aliquot, was stored under toluene at 4°C. Additional portions of the second aliquot were frozen at −20°C without preservatives for measurement of aldosterone, electrolytes, urea, creatinine, and total protein. Fasting serum was obtained each morning for measurement of creatinine and calculation of creatinine clearance ($ml \cdot min^{-1} \cdot 1.73\ m^2$).

After the last day of the low-protein diet and before the start of the high-protein diet, the responses of GFR and renal excretion of active kallikrein, prokallikrein, and kinins were measured after acute protein ingestion. Subjects remained fasting and supine in the morning and beginning at 0630 h drank 300 ml of water every 30 min. After 90 min, three 30-min base-line urine collections were obtained. They then ingested, over 15 min, 45 g of a commercial casein preparation dissolved in 300 ml water (Casec, Mead Johnson Nutritional Division, Evansville, IN). In 45 g Casec there are 40 g casein, 1 g fat, 720 mg calcium, 360 mg phosphorous, 2.9 meq sodium, 0.12 meq potassium, and 0.13 meq chloride. Water intake (300 ml) and urine collections continued each 30 min for 5 h after Casec ingestion. Active kallikrein, prokallikrein, kallikrein-like esterase activity, kinins, creatinine, sodium, potassium, and osmolality were measured in all urine collections. Urea was measured in the last base-line collection and the collection that was obtained 240–270 min after Casec (the period of maximum urine osmolality). Midway through each 30-min period, 1 ml blood was obtained through an indwelling intravenous cannula for measurement of microhematocrit and serum creatinine. Creatinine clearance was calculated for each period as $ml \cdot min^{-1} \cdot 1.73\ m^2$.

After 3–4 wk, five of the subjects underwent repeat acute studies either to assess urinary pH after protein ingestion or to determine the effect of water loading on renal kinin excretion. In the study of pH, voided urine was immediately drawn into a sealed syringe and pH was measured within 5 min. We previously determined that samples collected in this manner have the same pH as urine collected under oil.

*Assays.* Active kallikrein was measured directly in urine using a radioimmunoassay (29). The polyclonal antiserum used in this assay recognizes only the active enzyme. Prokallikrein was measured as the increase in active enzyme concentration after trypsin treatment, as previously described (30). Briefly, urine (10–20 μl) was added to 0.2 M tris(hydroxymethyl)aminomethane hydrochloride (Tris·HCl) buffer (pH 8.0; final volume 45 μl) and incubated at 37°C for 10 min with 1 μg trypsin diluted in 5 μl Tris·HCl buffer (type III trypsin from bovine pancreas; Sigma Chemical, St. Louis, MO). After incubation, the trypsin was inhibited by addition of 5 μl buffer containing 8 μg soybean trypsin inhibitor (type I; Sigma Chemical). Kallikrein in trypsin-treated samples is total kallikrein, and the prokallikrein content was derived by subtracting active kallikrein measured without trypsin treatment.

Urinary kallikrein-like esterase activity was measured as previously described, using [$^3$H]tosyl-arginine methyl ester substrate (29). Urinary kinins were measured by radioimmunoassay (28). Urinary aldosterone was measured by a commercial radioimmunoassay kit (Diagnostics Products, Los Angeles, CA). Serum and urine creatinine were measured by a kinetic method using alkaline picrate, modified from the Jaffe method (8). Urinary protein was measured with the Bio-Rad protein assay (Bio-Rad Laboratories, Richmond, CA). Urinary urea was measured by AutoAnalyzer (Astra-8, Beckman Instruments, Brea, CA). Urine sodium and potassium were measured by flame photometry using an IL943 analyzer (Instrumentation Laboratories, Newton, MA). Urine osmolality was measured with a vapor pressure osmometer (Wescore, Ogden, UT).

*Statistical analysis.* Data are expressed as means ± SE and were analyzed by analysis of variance for repeated measurements. Significance levels were adjusted using the Bonferroni method to reduce type I error due to multiple analyses.

## RESULTS

*Chronic effects of dietary protein.* Figure 1 shows GFR, measured as creatinine clearance, and the daily renal excretion rates of kinins, active kallikrein, and prokallikrein during the last 2 days of the 40-g protein diet and the 7 days of 140-g protein intake. GFR showed a gradual increase when protein intake was increased, and by *day 5* of high protein, GFR was significantly greater than on the last day of low protein intake (130 ± 10 vs. 117 ± 7 ml/min, $P < 0.03$). Renal kinin excretion increased significantly on *day 1* of high protein intake (26.0 ± 2.5 vs. 19.7 ± 1.2 μg/day on low-protein *day 7*, $P < 0.002$). Over the next 6 days, kinin excretion remained elevated, showing a slight further increase (high-protein *day 7*: 27.6 ± 2.9 μg/day, $P < 0.004$ vs. low-protein *day 7*). Taking the last 2 days of low-protein diet and 7 days of high-protein diet together, GFR was directly correlated with the kinin excretion rate ($r = 0.87$, $P < 0.01$).

Active kallikrein and prokallikrein excretion increased progressively during the high-protein diet. Compared

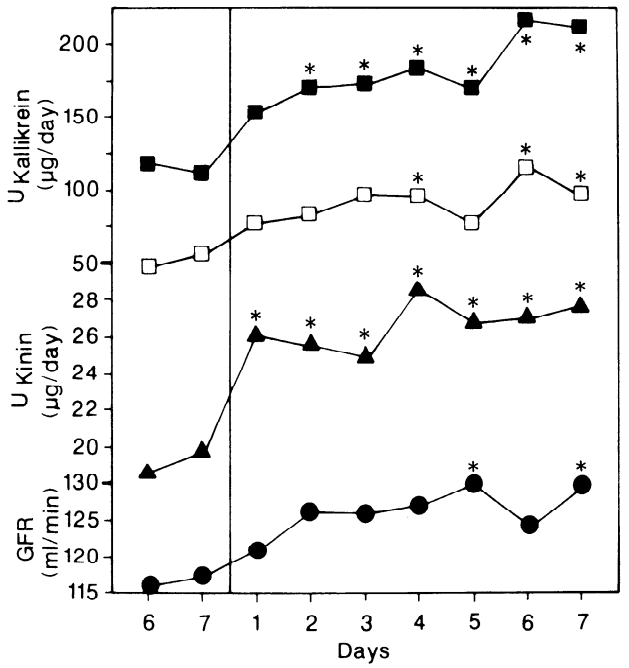


FIG. 1. Effects of dietary protein on glomerular filtration rate (GFR), urinary kinin ($U_{Kinin}$), active kallikrein (closed squares), and prokallikrein (open squares) excretion ($U_{Kallikrein}$). Values on *days 6* and *7* of low-protein diet (40 g) are plotted to left of vertical line, and *days 1–7* of high-protein diet (140 g) are plotted to right of line. * $P < 0.05$ or less.

TABLE 1. *Electrolyte, volume, and osmole excretion measured at end of low- and high-protein diets*

| Diet | $U_{Na}$, meq/day | $U_K$, meq/day | $U_V$, ml/day | $U_{osmol}$, mosmol/day |
|---|---|---|---|---|
| Low protein | 137±10 | 65±3 | 2,004±124 | 478±44 |
| High protein | 140±17 | 59±4 | 1,858±149 | 828±120* |

Values are means ± SE. $U_{Na}$, sodium excretion; $U_K$, potassium excretion; $U_V$, volume excretion; $U_{osmol}$, osmole excretion. Excretion rates on *days 6* and *7* of each diet period were averaged for each subject. * $P < 0.02$.

with the last day of low protein intake, urinary active kallikrein increased significantly by *day 2* of high protein intake (171 ± 40 vs. 111 ± 11 μg/day, $P < 0.006$). However, urinary prokallikrein did not show a significant increase until the 4th day of high protein intake (96.0 ± 38.2 vs. 55.5 ± 13.8 μg/day on low-protein *day 7*, $P < 0.003$). By the 6th high-protein day, both active kallikrein and prokallikrein excretion had doubled, compared with their excretion rates on *day 7* of low-protein diet.

Excretion rates of sodium and potassium on the last 2 days of the low-protein diet showed that the subjects were excreting nearly their dietary intake of these electrolytes (Table 1). Urinary sodium, potassium, and volume did not change during the subsequent 7 days when protein intake increased (average of last 2 days shown in Table 1). However, solute excretion, measured as urinary osmoles, increased nearly 75% (Table 1). The increase in solute excretion was primarily due to urea, which accounted for an increase of 200 mosmol/day (4.7 ± 0.4 g/day at the end of low-protein diet vs. 16.8 ± 1.3 g/day at the end of high-protein diet, $P < 0.001$). Total protein excretion was unchanged (54 ± 6 vs. 55 ± 7 mg/day). Urinary aldosterone excretion was also similar at the end of each diet period (10.9 ± 4.7 and 8.7 ± 2.3 μg/day, *day 7* of low and high protein intake, respectively). Finally, blood pressure did not change. Supine morning systolic pressure on the last 2 days averaged 110 ± 3 mmHg on low-protein diet and 108 ± 3 mmHg on the high-protein diet. Diastolic blood pressures were 75 ± 2 and 74 ± 3 mmHg, respectively.

*Acute effects of protein ingestion.* At the end of the week of low-protein diet, the acute effects of ingesting 40 g casein were studied (Fig. 2). After casein ingestion, GFR showed a progressive increase. An unexplained transient drop occurred between 120 and 150 min in three patients, but by 180 min GFR had increased significantly from base line in all patients (154 ± 18 vs. 131 ± 10 ml/min just before ingestion, $P < 0.005$). The increase in GFR was sustained over 90 min, returning toward base line by 4.5 h. Renal kinin excretion also increased progressively, and this increase was significant by 120 min after protein ingestion (586 ± 64 vs. 402 ± 33 pg/30 min, $P < 0.001$). This preceded the GFR increase by 60 min. When base-line and postcasein periods were taken together, GFR correlated directly with the kinin excretion rate ($r = 0.77$, $P < 0.01$).

In contrast to the sustained increase in active kallikrein excretion during chronic high protein intake, urinary active kallikrein fell, from 2.52 ± 0.50 μg/30 min just before ingestion to 2.05 ± 0.44 μg/30 min ($P < 0.05$) at 180 min after acute protein ingestion (Fig. 2). There was a transient increase apparent 30 min after protein ingestion, but this was insignificant. The excretion rate of prokallikrein showed no change throughout.

Urinary kallikrein-like esterase activity was measured to determine whether the fall in active kallikrein, as measured by radioimmunoassay, was associated with a change in enzymatic activity. Urinary esterase activity fell in parallel with immunoreactive kallikrein. The specific activity of urinary kallikrein was 11.2 ± 0.6 esterase

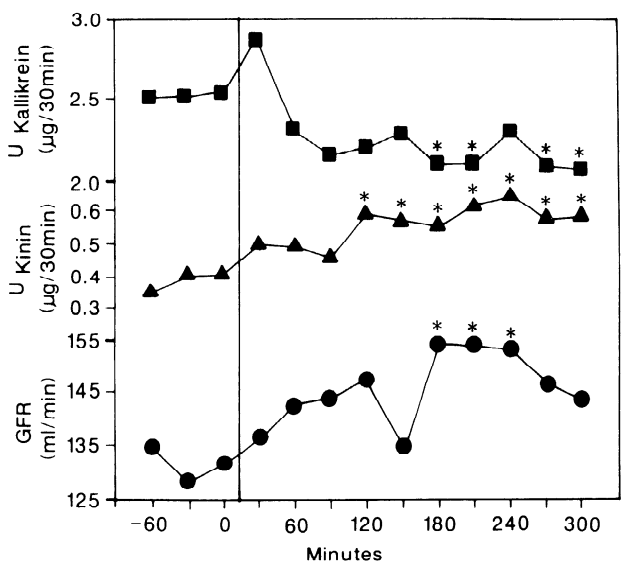


FIG. 2. Effects of acute protein ingestion on glomerular filtration rate (GFR), urinary kinin ($U_{Kinin}$), and active kallikrein excretion ($U_{Kallikrein}$). Values plotted at −60 to 0 min, left of vertical line, represent base line. Values plotted on right of line follow ingestion of 40 g casein (see METHODS for details). * $P < 0.05$ or less.

units/mg active kallikrein during base line and averaged 11.0 ± 1.5 between 180 and 300 min postprotein.

Excretion of osmoles and sodium increased 120 and 150 min, respectively, after casein ingestion (Fig. 3). Both remained elevated throughout the 5-h period of study. In contrast to the changes after chronic high protein intake, the increase in urea excretion after acute protein ingestion contributed only 20% (~2 mosmol) to the increase in solute excretion (urea preingestion, 229 ± 27 vs. 354 ± 49 mg/30 min at 270 min postingestion, $P < 0.05$). Sodium excretion contributed nearly 40% to the increase in urine solute. Potassium excretion showed a transient and significant fall between 60 and 150 min, returning to base line by 4 h. Urine volume did not change (Fig. 3), and hematocrit did not change from a base-line value of 44.4 ± 0.6%.

Five subjects were restudied to examine whether the increase in kinin excretion after acute protein ingestion could be due to the effects of oral water loading or the result of changes in urinary pH (27). If protein was not ingested, active kallikrein and kinin excretion, GFR, and urine volume showed no consistent change over a 7.5-h period of water intake at 300 ml/30 min. Average values during the time periods from −60 to 0 and 180 to 240 min are shown in Table 2. The rise in urinary kinins after protein ingestion was not associated with a concomitant change in urinary pH. Urine pH did increase during the pre-base-line period when water loading increased urine flow (5.48 ± 0.06 to 6.22 ± 0.11, $P < 0.03$). However, from the subsequent base-line period there was no significant pH change after protein ingestion (6.20 ± 0.15 to 6.43 ± 0.23, maximum postprotein).

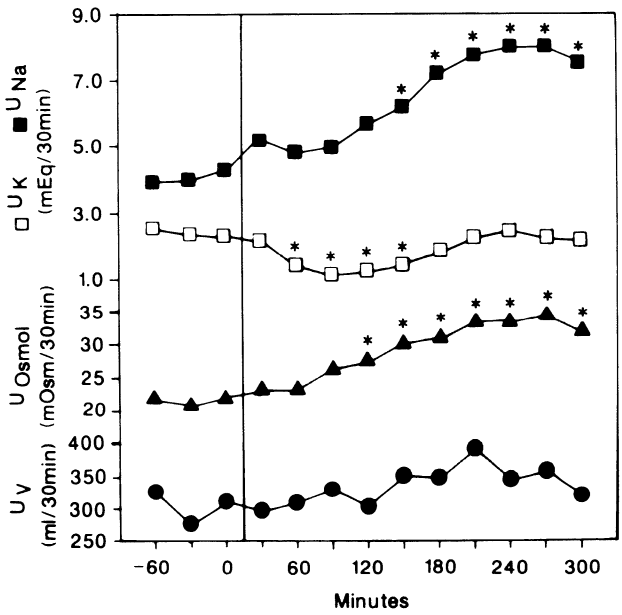


FIG. 3. Effects of acute protein ingestion on urinary volume ($U_v$), osmole excretion ($U_{osmol}$), and excretion of potassium ($U_k$, open squares) and sodium ($U_{Na}$, closed squares). Base-line and postprotein values are plotted as described in legend for Fig. 2. * $P < 0.05$ or less.

## DISCUSSION

These studies are the first to clearly show that dietary protein influences the renal kallikrein-kinin system in humans. Nearly 40 years ago, Frey et al. (12) found no change in kallikrein excretion in humans on high-meat vs. meatless diets, but they subsequently reported that egg protein ingestion increased urinary kallikrein activity (13). More recently, the excretion of kallikrein-like esterase activity was reported to be unchanged in macrobiotic vegetarians during 4 wk when beef was introduced into their diet (25). In none of these studies was total protein intake controlled.

In the present study, humans fed a low-protein diet for 7 days subsequently showed consistent urinary kinin and kallikrein responses to acute protein ingestion as well as to sustained high protein intake. Acutely, renal kinin excretion increased nearly 50% within 2 h after ingestion of 40 g casein, and this was followed within 1 h by a significant rise in GFR. When daily protein intake increased from 40 to 140 g/day, the daily kinin excretion rate increased 32% on the 1st day and remained increased over 7 days. Although 24-h creatinine clearance was not statistically increased until *day 5*, a progressive trend was apparent by the 2nd day of high-protein diet. In both acute and chronic studies, GFR and kinin excretion rate were directly correlated.

The GFR increase, measured by creatinine clearance, averaged 17.5% in the acute study and 11% in the chronic study. In two previous studies in which amino acid mixtures were given orally, inulin clearance acutely increased 8–10% (9, 31). After meat or mixed protein ingestion, 8–50% increases have been observed in inulin or creatinine clearance (4, 6, 9, 14, 31). Previous studies of chronic protein effects in normal subjects have observed a 15–27% increase in inulin or creatinine clearance when protein intake increased from a low level (20–40 g) to normal or high levels for 1–3 wk (4, 22, 33). A good correlation was found between changes in inulin and creatinine clearances in normal subjects ingesting protein or amino acids (4, 9). Together with another study showing that renal handling of creatinine is not altered by protein intake when renal function is normal (6), this provides support that the increase in creatinine clearance which we observed reflects an increase in GFR.

Although the urinary kinin response and its relation to GFR were similar after acute and chronic protein challenge, the kallikrein responses differed. In contrast

TABLE 2. *Urinary active kallikrein, kinin, volume, and GFR during water-loading control study*

| Time Periods, min | $U_{Kallikrein}$, μg/30 min | $U_{Kinin}$, pg/30 min | GFR, ml/min | $U_V$, ml/30 min |
|---|---|---|---|---|
| −60 to 0 | 4.19±0.45 | 418±24 | 131±9 | 317±24 |
| 180 to 240 | 4.35±0.16 | 375±55 | 136±7 | 328±23 |

Values are means ± SE. Time periods correspond to those shown in Fig. 2. Values for the 3 collections obtained during these periods were averaged for each patient. $U_{Kallikrein}$, kallikrein excretion; $U_{Kinin}$, kinin excretion; GFR, glomerular filtration rate; $U_V$, volume excretion.

to the increase in active kallikrein excretion during chronic high protein intake, acute protein ingestion produced a fall in urinary active kallikrein. It is also of interest that the excretion of active kallikrein was not significantly increased until *day 2* of high-protein diet, a day after kinin excretion increased. Urinary prokallikrein showed a more gradual increase.

The reasons for the disparity in urinary kallikrein response to acute vs. chronic protein challenge are not clear from our data. It is possible that changes in renal kallikrein activity are not disparate but that urinary excretion does not consistently reflect intrarenal concentrations. If the renal kallikrein-kinin system responds to protein ingestion to increase intrarenal kinins, the fall in active kallikrein excretion after acute ingestion could reflect early retention of enzyme to effect an acute increase in renal tissue activity. This could also explain why the subsequent rise in 24-h kallikrein excretion during continued high protein intake occurred more slowly than the rise in 24-h urinary kinins. Evidence that the increase in excretion of kallikrein with chronic high protein intake is likely to reflect increased intrarenal production comes from a recent study in rats showing that increased excretion of active and prokallikrein during 10–12 days of high-protein feeding is associated with increased renal prokallikrein synthesis (16a).

It is also possible that the rise in urinary kinins after acute protein digestion is not the result of increased intrarenal kallikrein activity but, rather, is due to decreased kinin degradation. This possibility is supported by a recent preliminary finding in low-protein-fed rats infused with amino acids. Total renal kininase activity is higher in low-protein-fed rats than in normal-protein-fed rats, and the activity falls acutely in response to amino acid infusion as urinary kinins rise (17). Changes in the availability of kininogen, the substrate for kinin generation, might also contribute to an increase in kinin levels. Clearly, the responses of all of the kallikrein-kinin system components to dietary protein requires further study.

Finally, a direct causal relationship between the kallikrein-kinin responses and the GFR response to protein is not demonstrated by our data. However, the findings are consistent with the notion that changes in kallikrein activity and kinin production could participate in mediating hemodynamic effects of protein on the kidney. More direct evidence for such an hypothesis was obtained in recent rat studies. Similar to the present observations in humans, in rats GFR and urinary kinins as well as RPF acutely increase during amino acid infusion, and sustained elevations occur during chronic high-protein feeding (16a, 17). All of these responses are blocked or reversed by administration of aprotinin, a kallikrein inhibitor (16a, 17). Moreover, treatment with a kinin receptor antagonist blocks the rise in GFR and RPF during amino acid infusion, whereas the kinin response persists (18).

Although kallikrein is produced in the distal nephron, where it is secreted into the lumen, several recent findings suggest that the enzyme or its generated kinins might have paracrine effects on the glomerulus. First, kallikrein is localized on basolateral membranes of connecting tubule cells that are within a few microns of the glomerular afferent arteriole (1, 34). Second, when applied to the antilumenal surface of glomerular arterioles, physiological kinin concentrations relax these vessels (10). Third, kinins stimulate eicosanoid production by afferent arterioles and mesangial cells (25, 32), and both kallikrein and kinins can release renin from isolated glomeruli (2, 3). Thus our findings raise the possibility that increases in kallikrein and kinins might be linked to increases in renal eicosanoid production and plasma renin that have been observed in response to high protein intake or amino acid infusion (20, 23, 24).

A role for kallikrein and kinins in protein-induced renal hemodynamic changes is not established, but the present data clearly demonstrate that altering dietary protein intake in humans produces acute and sustained changes in the urinary levels of this renal enzyme and its vasoactive peptide product.

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REFERENCES

1. BARAJAS, L., K. POWERS, O. A. CARRETERO, A. G. SCICLI, AND T. INAGAMI. Immunocytochemical localization of renin and kallikrein in the rat renal cortex. *Kidney Int.* 29: 965–970, 1986.
2. BEIERWALTES, W. H., J. PRADA, AND O. A. CARRETERO. Effects of glandular kallikrein on renin release in isolated rat glomeruli. *Hypertension Dallas* 7: 27–31, 1985.
3. BEIERWALTES, W. H., J. PRADA, AND O. A. CARRETERO. Kinin stimulation of renin release in isolated rat glomeruli. *Am. J. Physiol.* 248 (*Renal Fluid Electrolyte Physiol.* 17): F757–F761, 1985.
4. BOSCH, J. P., A. SACCAGGI, A. LAUER, C. RONCO, M. BELLEDONNE, AND S. GLABMAN. Renal functional reserve in humans: effect of protein intake on glomerular filtration rate. *Am. J. Med.* 75: 943–950, 1983.
5. CASTELLINO, P., W. HUNT, AND R. A. DEFRONZO. Regulation of renal hemodynamics by plasma amino acid and hormone concentrations. *Kidney Int.* 32, *Suppl.* 22: S15–S20, 1987.
6. CHAN, A. Y. M., M.-L. L. CHENG, L. C. KEIL, AND B. D. MYERS. Functional response of healthy and diseased glomeruli to a large protein-rich meal. *J. Clin. Invest.* 81: 245–254, 1988.
7. CHAPMAN, A., S. E. MULRONEY, J. F. WINCHESTER, L. LYNAM, AND A. HARAMATI. Serum atrial natriuretic peptide and urinary cyclic AMP are not influenced by water and protein loading in normal subjects (Abstract). *Clin. Res.* 36: 516A, 1988.
8. COOK, J. G. H. Creatinine assay in the presence of protein. *Clin. Chim. Acta* 32: 485–486, 1971.
9. DHAENE, M., J.-P. SABOT, Y. PHILIPPART, J.-M. DOUTRELEPONT, AND J.-L. VANHERWEGHEM. Effects of acute protein loads of different sources on glomerular filtration rate. *Kidney Int.* 32, *Suppl.* 22: S25–S28, 1987.
10. EDWARDS, R. M. Response of isolated renal arterioles to acetylcholine, dopamine, and bradykinin. *Am. J. Physiol.* 248 (*Renal Fluid Electrolyte Physiol.* 17): F183–F189, 1985.
11. EISENHAUER, T., J. TALARTSCHIK, AND F. SCHELER. Angiotensin converting enzyme inhibition by captopril reduces amino acid-mediated increase in glomerular filtration rate. *J. Hypertens.* 4, *Suppl.* 5: S258–S260, 1986.
12. FREY, E. K., H. KRAUT, AND E. WERLE. *Kallikrein (Padutin).*

Stuttgart, FRG: Enke, 1950, p. 25–27.
13. FREY, E. K., H. KRAUT, AND E. WERLE. *Das Kallikrein-Kinin System und seine Inhibitoren.* Stuttgart, FRG: Enke, 1968, p. 198–216.
14. HOSTETTER, T. H. Human response to a meat meal. *Am. J. Physiol.* 250 (*Renal Fluid Electrolyte Physiol.* 19): F613–F618, 1986.
15. HURA, C. E., AND R. T. KUNAU. Angiotensin II-stimulated prostaglandin production by canine afferent arterioles. *Am. J. Physiol.* 254 (*Renal Fluid Electrolyte Physiol.* 23): F734–F738, 1988.
16. ICHIKAWA, I., M. L. PURKERSON, S. KLAHR, J. L. TROY, M. MARTINEZ-MALDONADO, AND B. M. BRENNER. Mechanism of reduced glomerular filtration rate in chronic malnutrition. *J. Clin. Invest.* 65: 982–988, 1980.
16a. JAFFA, A. A., J. N. HARVEY, S. SUTHERLAND, H. S. MARGOLIUS, AND R. K. MAYFIELD. Renal kallikrein responses to dietary protein: a possible mediator of hyperfiltration. *Kidney Int.* In press.
17. JAFFA, A. A., AND R. K. MAYFIELD. Effects of inhibiting renal kinin production on amino acid-induced increase in glomerular filtration rate (GFR) and renal plasma flow (RPF) (Abstract). *Clin. Res.* 36: 520A, 1988.
18. JAFFA, A. A., J. M. STEWART, R. J. VAVREK, P. F. RUST, AND R. K. MAYFIELD. A bradykinin antagonist prevents the increase in glomerular filtration induced by aminoacids (Abstract). *Clin. Res.* 37: 492A, 1989.
19. KRISHNA, G. G., G. NEWELL, E. MILLER, P. HEEGER, R. SMITH, M. POLANSKY, S. KAPOOR, AND R. HOELDTKE. Protein-induced glomerular hyperfiltration: role of hormonal factors. *Kidney Int.* 33: 578–583, 1988.
20. LEVINE, M. M., M. A. KIRSCHENBAUM, A. CHAUDHARI, M. W. WONG, AND N. S. BRICKER. Effect of protein on glomerular filtration rate and prostanoid synthesis in normal and uremic rats. *Am. J. Physiol.* 251 (*Renal Fluid Electrolyte Physiol.* 20): F635–F641, 1986.
21. MEYER, T. W., I. ICHIKAWA, R. KATZ, AND B. M. BRENNER. The renal hemodynamic response to amino acid infusion in the rat. *Trans. Assoc. Am. Physicians* 96: 76–83, 1983.
22. PULLMAN, T. N., A. S. ALVING, R. J. DERN, AND M. LANDOWNE. The influence of dietary protein intake on specific renal functions in normal man. *J. Lab. Clin. Med.* 44: 320–331, 1954.
23. ROSENBERG, M. E., J. E. SWANSON, B. L. THOMAS, AND T. H. HOSTETTER. Glomerular and hormonal responses to dietary protein intake in human renal disease. *Am. J. Physiol.* 253 (*Renal Fluid Electrolyte Physiol.* 22): F1083–F1090, 1987.
24. RUILOPE, L. M., J. RODICIO, R. G. ROBLES, J. SANCHO, B. MIRANDA, J. P. GRANGER, AND J. C. ROMERO. Influence of a low sodium diet on the renal response to amino acid infusion in humans. *Kidney Int.* 31: 992–999, 1987.
25. SACKS, F. M., A. DONNER, W. P. CASTELLI, J. GRONENMEYER, P. PLETKA, H. S. MARGOLIUS, L. LANDSBERG, AND E. H. KASS. Effect of ingestion of meat on plasma cholesterol of vegetarians. *J. Am. Med. Assoc.* 246: 640–644, 1981.
26. SCHNERMANN, J., J. P. BRIGGS, G. SCHUBERT, AND M. MARIN-GREZ. Opposing effects of captopril and aprotinin on tubuloglomerular feedback responses. *Am. J. Physiol.* 247 (*Renal Fluid Electrolyte Physiol.* 16): F912–F918, 1984.
27. SCICLI, A. G., M. A. DIAZ, AND O. A. CARRETERO. Effect of pH and amiloride on the intrarenal formation of kinins. *Am. J. Physiol.* 245 (*Renal Fluid Electrolyte Physiol.* 14): F198–F203, 1983.
28. SHIMAMOTO, K., T. ANDO, T. NAKAO, S. TANAKA, M. SAKUMA, AND M. MIYAHARA. A sensitive radioimmunoassay method for urinary kinins in man. *J. Lab. Clin. Med.* 91: 721–728, 1978.
29. SHIMAMOTO, K., J. CHAO, AND H. S. MARGOLIUS. The radioimmunoassay of human urinary kallikrein and comparisons with kallikrein activity measurements. *J. Clin. Endocrinol. Metab.* 51: 840–848, 1980.
30. SHIMAMOTO, K., J. CHAO, AND H. S. MARGOLIUS. A method for determination of human urinary inactive kallikrein (prekallikrein). *Tohoku J. Exp. Med.* 137: 269–274, 1982.
31. SOLLING, K., C. K. CHRISTENSEN, J. SOLLING, J. S. CHRISTIANSEN, AND C. E. MOGENSEN. Effect on renal haemodynamics, glomerular filtration rate and albumin excretion of high oral protein load. *Scand. J. Clin. Lab. Invest.* 46: 351–357, 1986.
32. UGLESITY, A., J. I. KREISBERG, AND L. LEVINE. Stimulation of arachidonic acid metabolism in rat kidney mesangial cells by bradykinin, antidiuretic hormone and their analogues. *Prostaglandins Leukotrienes Med.* 10: 83–93, 1983.
33. VIBERTI, G., E. BOGNETTI, M. J. WISEMAN, R. DODDS, J. L. GROSS, AND H. KEEN. Effect of protein-restricted diet on renal response to a meat meal in humans. *Am. J. Physiol.* 253 (*Renal Fluid Electrolyte Physiol.* 22): F388–F393, 1987.
34. VIO, C. P., AND C. D. FIGUEROA. Subcellular localization of renal kallikrein by ultrastructural immunocytochemistry. *Kidney Int.* 28: 36–42, 1985.