Effect of Protein Intake on Regional Vascular Resistance and Reactivity to Angiotensin II in the Rat

Brian M. Murray

Male Sprague-Dawley rats (200–250 g) were fed low protein (6%) diets (LP rats), high protein (50%) diets (HP rats), or regular rat chow (~16% protein) (control rats) and studied under anesthesia after 2 weeks. Dietary protein intake did not affect mean arterial pressure, but renal blood flow was increased in the HP rats and decreased in the LP rats compared with the control rats. Mesenteric blood flow was not significantly different in the three diet groups. Captopril (10 mg · kg⁻¹ i.v.) had no effect on renal vascular resistance in the HP rat but did reduce the elevated renal vascular resistance seen in the LP rat. Meclofenamate (5 mg · kg⁻¹ i.v.) did not significantly affect renal hemodynamics in either HP or LP rats. Finally, the HP rat exhibited resistance to the systemic pressor, renal, and mesenteric vasoconstrictor effects of angiotensin II. Captopril restored the systemic pressor and the mesenteric vasoconstrictor response but not the renal vasoconstrictor response to angiotensin II. Meclofenamate, on the other hand, restored both the systemic pressor response and the renal vasoconstrictor response. Thus, in the LP rat, the vascular response to angiotensin II remains intact, and renal vasoconstriction appears to be mediated by angiotensin II. In contrast, in the HP rat, the renovascular response to angiotensin II is blunted apparently because of enhanced renal prostaglandin production. However, neither increased renal prostaglandin synthesis nor blunting of the renovascular response to angiotensin II appears to account for the chronic vasodilation seen in the HP rat. (Circulation Research 1990;67:440–447)

Increasing dietary protein intake has been shown to result in increased renal mass, renal blood flow (RBF), and glomerular filtration rate in both experimental animals1–4 and man.5 Interest in the renal hemodynamic response to protein stems not only from a desire to understand the normal control of renal function but also from the recently proposed hypothesis that dietary protein may damage the kidney, especially if it is already injured.6 The detrimental effect of protein appears to be a consequence of increased flows and pressures induced in the glomerular microcirculation, but the mechanism by which protein intake produces these effects remains poorly understood.6

Paller and Hostetter7 have shown that rats fed a high protein diet exhibit increased plasma renin activity, increased urinary excretion of vasodilatory prostaglandins, and resistance to the systemic pressor response to angiotensin II (Ang II). Other investigators8,9 have also shown evidence of increased prostaglandin synthesis in the kidneys of rats fed a high protein diet. Recent data from both animal8 and human10 studies have suggested that the increase in glomerular filtration rate seen after acute ingestion of a protein load may be mediated by prostaglandins. It is not known whether the mechanisms responsible for the sustained increases in RBF and glomerular filtration seen in animals chronically maintained on a high protein diet are similar to those seen after acute ingestion of a protein meal. The purpose of this study was to investigate the role of the renin-angiotensin and prostaglandin systems in the altered baseline hemodynamics induced by changes in protein intake and to determine whether protein intake altered vascular reactivity to Ang II. Studies were performed in two distinct vascular beds, the renal and mesenteric circulations.
TABLE 1. Effect of Dietary Protein Intake on Weight, Hematocrit, Mean Arterial Pressure, Renal Blood Flow, and Renal Vascular Resistance in Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (g)</th>
<th>Hct (%)</th>
<th>MAP (mm Hg)</th>
<th>RBF (ml \cdot min^{-1})</th>
<th>RVR (mm Hg \cdot ml^{-1} \cdot min^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=7)</td>
<td>297±6†</td>
<td>0.47±0.01</td>
<td>107±4</td>
<td>7.0±0.2‡</td>
<td>15.2±0.5‡</td>
</tr>
<tr>
<td>2 (n=7)</td>
<td>252±5‡</td>
<td>0.47±0.02</td>
<td>112±6</td>
<td>4.7±0.2‡</td>
<td>24.8±1.6‡</td>
</tr>
<tr>
<td>3 (n=6)</td>
<td>318±6</td>
<td>0.46±0.01</td>
<td>116±5</td>
<td>5.8±0.3</td>
<td>20.1±1.0</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Hct, hematocrit; MAP, mean arterial pressure; RBF, renal blood flow; RVR, renal vascular resistance; group 1, rats fed a high protein (50%) diet; group 2, rats fed a low protein (6%) diet; group 3, rats fed standard rat chow (16% protein content). No significant differences were found between groups for Hct and MAP values.

*P<0.01 compared with group 2 by analysis of variance (ANOVA).
†P<0.05 compared with group 3 by ANOVA.
‡P<0.01 compared with group 3 by ANOVA.

Materials and Methods

Male Sprague-Dawley rats (Charles River Laboratories, Inc., Wilmington, Mass.) weighing 200–250 g were housed in metabolic cages with free access to food and drinking water and were divided into three dietary groups. Rats were fed standard rat chow (16% protein) (control rats), a high protein (50%) diet (HP rats), or a low protein (6%) diet (LP rats). The diets (Teklad Test Diets, Madison, Wis.) were isocaloric with identical mineral composition and differed only in protein and carbohydrate content. Physiological studies were performed after a mean of 2 weeks on the special diets (range, 12–17 days).

For hemodynamic studies, rats from each dietary group were anesthetized with 100 mg/kg i.p. Inactin (Byk Gulden, Konstang, FRG) and placed on a heated operating table to maintain body temperature at 37°C throughout. A tracheostomy was performed, and saline (0.9% NaCl) was infused continuously into a jugular vein at a rate of 34 μl/min via a polyethylene (PE-50) catheter. Similar catheters were also placed in the femoral artery to monitor mean arterial pressure (MAP) using a pressure transducer (Bell and Howell, Pasadena, Calif.) and in the femoral vein to administer drugs. For studies of the renal circulation (groups 1–3 in Table 1), the left kidney was then exposed via a midabdominal incision, and the left renal artery was isolated by gentle dissection. A small-diameter noncannulating electromagnetic flow probe (model EP 101.5, Carolina Medical Electronics, King, N.C.) with a 1.5-mm circumference (lumen size) connected to a square-wave electromagnetic flowmeter (model 501, Carolina Medical Electronics) was placed on the left renal artery for continuous monitoring of RBF. The outputs from the flowmeter and the pressure transducer were displayed simultaneously on a dynograph (model R411, Beckman, Schiller Park, Ill.). Values for renal vascular resistance (RVR) were derived from the following equation (in millimeters mercury per milliliter per minute): RVR=MAP+RBF. This equation assumes that renal venous pressure is too low to significantly influence the equation.

For studies of the mesenteric circulation (groups 4–6 in Table 2), a midline abdominal incision was again performed, and the bowel was gently mobilized, delivered out of the abdominal cavity, and wrapped in saline-soaked gauze. The mesenteric artery was then isolated by gentle dissection and fitted with an electromagnetic flow probe (model 102, Carolina Medical Electronics) with a 2.0-mm circumference (lumen size). Values of mesenteric blood flow (MBF) and mesenteric vascular resistance (MVR) were recorded as outlined above for the renal circulation. After surgery, a recovery period of 60 minutes was allowed before further studies. In separate studies in normal Sprague-Dawley rats, the maneuver of externalizing the bowel was not found to alter either resting vascular tone or the vasoconstrictor response to Ang II.

After the establishment of baseline MAP and RBF (or MBF) by averaging the values recorded over a 5-minute period, serial infusions of increasing doses of Ang II (Hypertensin, CIBA Pharmaceutical Co., Summit, N.J.) diluted in 5% dextrose/water were administered at a rate of 0.102 ml \cdot min^{-1} using an infusion pump (Harvard Apparatus, South Natick, Mass.). Five different doses were administered to each rat: 62.5, 125, 250, 375, and 500 ng \cdot kg^{-1} \cdot min^{-1} Ang II. Preliminary studies showed that administration of 5% dextrose/water at a rate of 0.102 ml \cdot min^{-1} for 5 minutes had no significant effect on MAP, RBF, or RVR. A sufficient period (usually about 10 minutes) was allowed between infusions to permit MAP and RBF (or MBF) to return to baseline values before administration of the next dose. This protocol resulted in essentially stable values for MAP, RBF (or MBF), and hematocrit throughout the experi-

TABLE 2. Effect of Dietary Protein Intake on Mesenteric Blood Flow in Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP (mm Hg)</th>
<th>MFB (ml \cdot min^{-1})</th>
<th>MVR (mm Hg \cdot ml^{-1} \cdot min^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (n=6)</td>
<td>112±3</td>
<td>17.0±1.4</td>
<td>6.8±0.5</td>
</tr>
<tr>
<td>5 (n=6)</td>
<td>105±7</td>
<td>14.3±0.5</td>
<td>7.6±0.6</td>
</tr>
<tr>
<td>6 (n=6)</td>
<td>110±6</td>
<td>14.5±2.0</td>
<td>8.1±0.9</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MAP, mean arterial pressure; MBF, mesenteric blood flow; MVR, mesenteric vascular resistance; group 4, rats fed a high protein (50%) diet; group 5, rats fed a low protein (6%) diet; group 6, rats fed standard rat chow (16% protein content). No significant differences were found between groups for MAP, MBF, or MVR values.
mental period. The MAP, RBF (or MBF), and RVR (or MVR) responses for each infusion rate were calculated as the difference between the mean values for these parameters during the final 60 seconds of the infusion and the mean values during the 60 seconds preceding the infusion. Regional vasoconstrictor responses to Ang II in both the renal and mesenteric circulations were expressed as the percentage increments in RVR or MVR. Since all the doses of Ang II that were used resulted in detectable rises in MAP, changes in RBF (or MBF) are difficult to interpret because decreases due to vasoconstriction may be counteracted by the increased perfusion pressure. Because the systemic and regional vascular responses to Ang II were not different in LP and control rats (see “Results”), a group of control rats was not included in subsequent experiments.

**Renal Hemodynamic Response to Ang II During Aortic Constriction**

All the infused doses of Ang II resulted in significant increments in MAP and, therefore, renal perfusion pressure (RPP). Therefore, the renal vascular response would be expected to include two components, a direct vasoconstrictor response to Ang II as well as an additional “autoregulatory” vasoconstriction in response to the elevated RPP. HP rats (n = 5) and LP rats (n = 5) were anesthetized and prepared as above except that an adjustable constrictor clamp was applied to the abdominal aorta above the renal arteries. After the usual equilibration period and after baseline MAP, baseline RBF, and baseline RVR (RVR_b) measurements, Ang II was infused at 250 ng · kg⁻¹ · min⁻¹. Once the MAP and RBF responses in the presence of elevated RPP (MAP_pre and RBF_pre, respectively) had stabilized, RPP was restored to pre-Ang II baseline values by constricting the suprarenal aorta. The new levels of MAP and RBF in the absence of elevated RPP (MAP_post and RBF_post, respectively) were then recorded. The renal vascular response (ΔRVR) could then be calculated both in the presence of elevated RPP (ΔRVR_pre) and in the absence of elevated RPP (ΔRVR_post):

\[
\%\Delta RVR_{pre} = \left( \frac{MAP_{pre} - RVR_{B}}{RVR_{B}} \right) \times 100
\]

\[
\%\Delta RVR_{post} = \left( \frac{MAP_{post} - RVR_{B}}{RVR_{B}} \right) \times 100
\]

**Systemic Renal and Mesenteric Hemodynamic Response to Ang II After Converting Enzyme Inhibition**

To determine the systemic, renal, and mesenteric responses to infused Ang II in the absence of endogenous production of the hormone, HP and LP rats were prepared with flow probes on the renal (or mesenteric) artery as outlined above. Forty-five minutes after completion of surgery, 5% dextrose vehicle (groups 7 and 8 in Table 3) or 10 mg/kg i.v. captopril (groups 9 and 10 in Table 3) was administered. Beginning 15 minutes later, the MAP and RBF (or MBF) responses to serial infusions of Ang II were determined. In preliminary studies, this dose of captopril was found to inhibit, by 80% or more, changes in MAP and RVR after a bolus dose of 200 ng angiotensin I, for at least 75 minutes, a period of time sufficient to complete the dose-response studies.

**Systemic and Renal Hemodynamic Response to Ang II After Inhibition of Prostaglandin Synthesis**

To determine the systemic and renal responses to Ang II after suppression of endogenous prostaglandin production, HP and LP rats were given 5 mg/kg i.v. meclofenamate in sodium carbonate (groups 13 and 14, respectively, in Table 4) 30 minutes after surgical preparation and placement of a renal artery flow probe; after the administration of meclofenamate, 30 minutes more was allowed to elapse before performing dose-response studies to serial Ang II infusions, as outlined above. Two other groups of HP and LP rats were given similar volumes of sodium carbonate vehicle (groups 11 and 12, respectively, in Table 4) to confirm that the vehicle did not affect baseline hemodynamics or the systemic or renal vasoconstrictor responses to Ang II. The dose of meclofenamate chosen has been shown to be adequate to inhibit renal prostaglandin synthesis.11

**Measurement of Extracellular Volume in Rats on High and Low Protein Diets**

To evaluate the possibility that a high or low protein diet might alter volume status, extracellular fluid volume was measured using [¹⁴C]inulin. Inulin equilibrates with the extracellular fluid so that its volume of distribution is a measure of extracellular fluid volume.
fluid volume. Preliminary experiments established that distribution of a bolus injection of $[^3H]$inulin was complete by 30 minutes and that subsequently elimination was linear; thus, single compartment kinetics could be used: metabolic clearance rate = $V_D\lambda$, where $V_D$ is the volume of distribution of $[^3H]$inulin and $\lambda$ is the fractional removal rate $=0.693/t\frac{1}{2}$.

A 1 $\mu$Ci bolus of $[^3H]$inulin was injected into anesthetized rats prepared as for hemodynamic studies, and 25-$\mu$l samples of blood were obtained at 30, 45, 60, 75, and 90 minutes, added to 10 ml scintillation fluid, and counted in a beta counter. A 25-$\mu$l aliquot of $[^3H]$inulin was simultaneously counted to obtain an estimate of injected counts. Log$_{10}$ counts per milliliter per minute at various sampling times were plotted against time using linear regression to determine the best fit: slope of the line $=\lambda$ while $V_D=D/C_0$, where $D$ is the activity of $[^3H]$inulin injected and $C_0$ is counts per milliliter per minute at time zero. $V_D$ was expressed as milliliters per kilogram of rat body weight.

All data are reported as mean±SEM. Comparisons between two groups were made by unpaired $t$ test. Comparisons between multiple groups were made using one-way analysis of variance, and the Studentized range test was then used for intergroup comparison.

### Results

The effect of the experimental diets on rat weight, hematocrit, and baseline hemodynamics are outlined in Table 1. All three dietary groups gained weight, but weight gains were less in both HP and LP rats compared with control rats; LP rats gained the least. Similar results have been found by others using identical diets and are not accounted for by differences in the amount of food eaten. No difference was found in extracellular fluid volume between HP and LP rats when measured as the volume of distribution of $[^3H]$inulin (791±126 ml/kg body wt for HP rats and 524±56 ml/kg body wt for LP rats, $n=7$, $p=NS$).

There was no difference in baseline MAP between the three dietary groups. RBF was significantly higher and RVR was lower in HP rats compared with control rats; the reverse was true for LP rats, who exhibited a significant decrease in RBF and rise in RVR. No significant differences were seen in MBF and MVR between HP, LP, and control rats (Table 2).

The systemic pressor, renal, and mesenteric responses to serial infusions of Ang II in HP, LP, and control rats are shown in Figure 1. The systemic pressor response was clearly reduced in the HP rats when compared with the LP rats. The altered response appears to be that of the HP rat, since the

### Table 4. Effect of Inhibition of Prostaglandin Synthesis on Systemic and Renal Hemodynamics in Rats Fed High and Low Protein Diets

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>MAP (mm Hg)</th>
<th>RBF (ml·min$^{-1}$)</th>
<th>RVR (mm Hg·ml$^{-1}$·min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (n=7)</td>
<td>Vehicle</td>
<td>117±6†</td>
<td>8.2±0.4‡</td>
<td>14.3±0.9‡</td>
</tr>
<tr>
<td>12 (n=7)</td>
<td>Vehicle</td>
<td>122±5§</td>
<td>4.9±0.4§</td>
<td>26.0±2.0§</td>
</tr>
<tr>
<td>13 (n=6)</td>
<td>Meclofenamate</td>
<td>108±4§</td>
<td>6.8±0.3¶</td>
<td>16.8±1.0¶</td>
</tr>
<tr>
<td>14 (n=6)</td>
<td>Meclofenamate</td>
<td>127±4</td>
<td>5.6±0.2</td>
<td>22.8±1.1</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MAP, mean arterial pressure; RBF, renal blood flow; RVR, renal vascular resistance; groups 11 and 13, rats fed a high protein (50%) diet; groups 12 and 14, rats fed a low protein (6%) diet.

* $p=NS$ compared with group 12 by analysis of variance (ANOVA).
†$p<0.01$ compared with group 12 by ANOVA.
‡$p=NS$ compared with group 13 by ANOVA.
§$p<0.05$ compared with group 14 by ANOVA.
¶$p<0.01$ compared with group 14 by ANOVA.

### Figure 1. Graphs showing systemic pressor (left panel), renal (middle panel), and mesenteric (right panel) responses to infusion of serial doses of angiotensin II in control rats (CON), rats fed a low protein diet (LP), and rats fed a high protein diet (HP). *Significant difference at the level of $p<0.01$ between HP compared with CON and LP.
responses of LP rats did not differ significantly from those of control rats. HP rats also showed lesser percentage increments in RVR and MVR in response to Ang II, suggesting that the renal and mesenteric vasoconstrictor responses were also impaired in these rats. As outlined earlier, the renal vascular response to Ang II includes two components, a direct vasoconstrictor response and an autoregulatory response. Figure 2 shows the effect of normalization of RPP during Ang II infusion (250 ng · kg⁻¹ · min⁻¹) on the renal vasoconstrictor response. The renal vasoconstrictor response was lower in both LP and HP rats after returning RPP to baseline values, which was consistent with the occurrence of some reflex vasoconstriction in response to the increased RPP during Ang II infusion. The most important finding, however, is that the response of the HP rat was still significantly lower than that of the LP rat, even after removal of the autoregulatory component, suggesting that renal refractoriness to Ang II in the HP rat reflected a true blunting of the renal vasoconstrictor response.

The effect of acute inhibition of converting enzyme with captopril on baseline hemodynamics in HP and LP rats is shown in Table 3. Captopril decreased MAP similarly in both HP and LP rats. RVR was not affected by captopril in HP rats but did fall in LP rats to the levels observed in HP rats. Figure 3 shows the pressor, renal, and mesenteric vasoconstrictor responses to Ang II after captopril. It shows that, although captopril restored the systemic pressor and mesenteric vasoconstrictor responses to Ang II in HP rats, the renal vascular bed remained refractory to the effects of Ang II.

Table 4 shows the effect of the cyclooxygenase inhibitor meclofenamate on baseline hemodynamics in HP and LP rats; the systemic pressor and renal vasoconstrictor responses to Ang II after meclofenamate are seen in Figure 4. Acute administration of meclofenamate did not significantly affect either MAP, RBF, or RVR in either HP or LP rats. RVR remained higher in LP compared with HP rats. Inhibition of prostaglandin synthesis did have a profound effect on vascular responses to Ang II in HP rats—both the systemic and renovascular responses to Ang II were restored to normal.

**Discussion**

Previous studies have shown that increased intake of dietary protein increases plasma renin activity and urinary excretion of vasodilator prostaglandins and results in blunting of the pressor response to Ang II in conscious animals. The purpose of this study was, therefore, to examine the role of the renin-angiotensin and prostaglandin systems in mediating changes in baseline hemodynamics induced by changes in dietary protein intake. The results confirm the tendency for RBF to increase on a high protein diet. This vasodilatation occurred despite evidence that plasma renin activity is enhanced in this state and was accompanied by resistance to the pressor and regional vasoconstrictor effects of Ang II. On the other hand, rats fed a low protein diet were characterized by a state of relative renal vasoconstriction with intact systemic and regional vascular responses to Ang II.

**FIGURE 2.** Bar graph showing renal vasoconstrictor response to infusion of angiotensin II (250 ng · kg⁻¹ · min⁻¹) before and after normalization of renal perfusion pressure by constriction of a suprarenal aortic clamp. LP, rats fed a low protein diet; HP, rats fed a high protein diet.

**FIGURE 3.** Graphs showing systemic pressor (left panel), renal (middle panel), and mesenteric (right panel) responses to infusion of serial doses of angiotensin II after administration of the converting enzyme captopril (CEI) in rats fed a low protein diet (LP+CEI) and in rats fed a high protein diet (HP+CEI). *Significant difference at p<0.05 between HP+CEI compared with LP+CEI.
To assess the role of changes in the renin-angiotensin system on the effects observed, endogenous production of Ang II was inhibited by administration of the converting enzyme inhibitor captopril. Captopril caused a profound hypotensive response in both HP and LP rats, suggesting that Ang II was important in the maintenance of systemic vascular resistance in anesthetized HP and LP rats; this response was unlike that of conscious animals, in which no fall in MAP with captopril was seen.7 No effect of captopril on RVR was seen in the HP rats, but RVR returned to normal in the LP rats that were given captopril. This suggests that vasoconstriction in the LP rat might be mediated by Ang II. These results are thus in agreement with the recent findings of Fernandez-Repollet et al,12 who also found normalization of both glomerular filtration rate and RBF in LP rats after chronic administration of captopril.

However, other explanations are possible. Captopril has been shown to increase plasma levels13 and renal synthesis14 of prostaglandins, and inhibitors of prostaglandin synthesis can blunt the hypotensive effect of captopril.15 Converting enzyme is also a kininase, and captopril results in increased kinin excretion in the dog.16 Thus, it is possible that increases in either vasodilatory prostaglandins or kinins could have mediated the changes in RVR seen after captopril in the LP rat.

Captopril did not affect baseline RVR in the HP rat. On the other hand, it did restore the systemic pressor and mesenteric vasoconstrictor responses to Ang II in HP rats. These observations suggest that elevated circulating levels of Ang II might be important in mediating systemic vascular resistance to Ang II in HP rats. Similar findings have been described in sodium depletion, in which both down-regulation of Ang II receptors17,18 or prior occupancy of these receptors by endogenous Ang II18 have been proposed as possible mechanisms. The protocol of acute converting enzyme inhibition used here was designed to test the second of these two possibilities, but an effect of captopril on receptor number cannot be completely excluded. However, previous studies7 have not provided any evidence of down-regulation of Ang II receptors in the HP rat, at least in the mesenteric circulation.

Paller and Hostetter7 were unable to normalize the systemic pressor response to Ang II in conscious HP rats by administration of captopril in the drinking water for 3 days before the study. It is not clear why their results differed from those reported here, but there were technical differences between the studies; they used conscious animals, and Ang II was given by bolus administration rather than as an infusion. The correction of the systemic Ang II response by captopril in the HP rat together with the higher plasma renin activity levels, which have been found by others,7 raise the possibility that HP rats may have been volume-depleted with respect to the LP rat. Extracellular fluid volume was, therefore, measured by an indicator dilution method using [3H]ulin, but no significant difference was found between HP and LP rats. When any difference existed, fluid volume tended to be higher in the HP rat. This is in agreement with the studies of Seney and Wright,20 who found no significant effect of increased dietary protein intake on plasma volume. Despite the improvement in the systemic pressor and mesenteric responses to Ang II seen in this study in HP rats after captopril, this maneuver did not restore the responsiveness of the renal circulation in these rats, suggesting a different mechanism for the decreased response of the renal circulation to Ang II after a high protein diet.

The lack of effect of acute meclofenamate administration on baseline RVR in the HP rat would seem to imply that vasodilatory prostaglandins are not involved in the hyperemic response to an increased protein intake. However, this response probably involves both structural (arteries of larger diameter) as well as functional (vasodilator) components, and although vasodilator prostaglandins could be involved in both, only the latter component would be expected to respond to acute meclofenamate administration. Inhibition of prostaglandin synthesis by meclofenamate did, however, restore both the systemic and renal responsiveness to Ang II. Restoration of the renal response by meclofenamate but not captopril suggests that enhanced renal prostaglandin production was a more important factor in mediating resistance to Ang II in the renal vasculature than were elevated circulating levels of Ang II and further suggests that the effect of meclofenamate was not mediated indirectly by its ability to decrease renin release.21 High dietary protein intake is known to stimulate urinary excretion of both prostaglandin E₂.
and 6-ketoprostaglandin F$_{1\alpha}$, the principal metabolite of prostacyclin, whereas acute protein loading in the rat has been shown to stimulate glomerular production of vasodilatory prostanooids. That such stimulation is primary and not secondary to activation of the renin-angiotensin system is suggested by the fact that urinary prostaglandin excretion actually increased after chronic administration of captopril to HP rats.

Finally, the fact that both captopril and meclofenamate restored the systemic pressor response to Ang II requires an explanation. This is most consistent with a role for elevated circulating Ang II in mediating systemic resistance to Ang II. Prostaglandin synthetase inhibitors are known to be capable of suppressing renin release. A precedent for the normalization of the systemic pressor response by both captopril and meclofenamate exists in the pregnant rabbit, another state characterized by stimulation of both the renin-angiotensin and prostaglandin systems.

It is of considerable interest that resistance to the systemic pressor and renal vasoconstrictor responses to Ang II appears to be mediated by different mechanisms. The systemic pressor response reflects the sum of the constrictions of all the vascular beds. Mesenteric resistance to Ang II was corrected by captopril, thus mirroring the behavior of the systemic pressor response. This supports the idea that the effects of protein on the renal vascular bed and the hormonal systems controlling it may be unique. Recent findings have led to considerable revision of the classic concept of the renin-angiotensin system as a systemic endocrine system to one of a two-tiered system consisting of circulating and tissue components. The primary function of the circulating renin-angiotensin system may not be the systemic delivery of Ang II to tissues but rather the delivery of renin and angiotensinogen to tissues. Ang II is then generated locally by the action of plasma-derived or locally synthesized renin on plasma-derived angiotensinogen and tissue-converting enzyme. In light of these considerations, it may not be surprising to find different mechanisms of Ang II resistance occurring in different vascular beds of the same animal.

In summary, a high protein diet resulted in renal vasodilatation, and a low protein diet resulted in renal vasoconstriction in Inactin-anesthetized rats, effects that appear to be selective for the renal circulation in that similar changes were not seen in mesenteric blood flow. HP rats also exhibited resistance to the systemic pressor response to Ang II, which was also reflected by decreased vasoconstrictor responses to Ang II in the renal and mesenteric vascular beds. Inhibition of the renin-angiotensin system by captopril had no effect on RVR in the HP rat but did reduce the elevated RVR seen in the LP rat. These findings suggest that, despite decreased systemic levels of circulating plasma renin activity, increased activity of the renin-angiotensin system may be important in maintaining the elevated renal vascular resistance seen in LP rats. Since meclofenamate had no effect on renal hemodynamics in either the HP or LP rat, the data do not support a role for vasodilatory prostaglandins in mediating the sustained renal vasodilatation seen in HP rats. Meclofenamate, but not captopril, restored the renal vasoconstrictor response to Ang II in the HP rat, suggesting that enhanced prostaglandin production was responsible for mediating the resistance of the renal circulation of these rats to this hormone. Both captopril and meclofenamate restored the systemic pressor and mesenteric vasoconstrictor responses to Ang II, effects most consistent with a role for elevated circulating levels of Ang II in mediating resistance to Ang II in other circulatory beds of the HP rat. Thus, alterations in dietary protein intake appear to have major effects on the delicate balance between the renin-angiotensin and prostaglandin systems, and these effects may vary from one vascular bed to another.

Acknowledgments

The author would like to thank Sandra Fuzak for her help in the preparation of the manuscript and Frank G. Ditz and Anna Ingeana for technical assistance. The captopril and meclofenamate used were gifts of E. R. Squibb & Sons, Inc. and Parke-Davis, respectively.

References


KEY WORDS • dietary protein • angiotensin II • renal circulation • mesenteric circulation • prostaglandins
Effect of protein intake on regional vascular resistance and reactivity to angiotensin II in the rat.

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Circ Res. 1990;67:440-447
doi: 10.1161/01.RES.67.2.440

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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