Kinin influences on renal regional blood flow responses to angiotensin-converting enzyme inhibition in dogs

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OMORO, Sophia A., Dewan S. A. Majid, Samir S. El-Dahr, and L. Gabriel Navar. Kinin influences on renal regional blood flow responses to angiotensin-converting enzyme inhibition in dogs. Am. J. Physiol. 276 (Renal Physiol. 45): F271–F277, 1999.—The relative roles of ANG II and bradykinin (BK) in the regulation of renal medullary circulation have remained unclear. We compared the contributions of ANG II and BK to the renal medullary blood flow (MBF) responses to angiotensin-converting enzyme (ACE) inhibition (enalaprilat, 33 µg·kg⁻¹·min⁻¹) in dogs maintained on a normal-salt diet (0.63%, 3 days, n = 14; group 1) with those fed a low-salt diet (0.01%, 5 days, n = 14; group 2), which upregulates both the kallikrein-kinin and the renin-angiotensin systems. MBF responses to ACE inhibition were evaluated either before (n = 7) or after (n = 7) treatment with the BK B₂ receptor blocker icatibant (100–300 µg) in both groups.

Laser-Doppler needle flow probes were used to determine relative changes in MBF and cortical blood flow (CBF). ACE inhibition increased MBF (group 1, 33 ± 9%, P ≤ 0.01; group 2, 24 ± 9%, P ≤ 0.005) as well as CBF (group 1, 23 ± 2%, P ≤ 0.006; group 2, 28 ± 10%, P ≤ 0.05). These responses were prevented by prior blockade of B₂ receptors in group 2, but not in group 1. These data indicate that under normal sodium intake, increases in MBF and CBF caused by ACE inhibition are primarily due to reduced intrarenal ANG II levels. In contrast, the renal vasodilatory responses to ACE inhibition in dogs on low salt intake were markedly dependent on the activation of BK B₂ receptors.

A substantive contributory role of BK receptor activation in the renal vasodilatory responses to ACE inhibitors, particularly in the medullary circulation, has also been reported. Mattson and Roman (16) reported that although infusion of ANG II in hypovolemic Munich-Wistar rats reduced captopril induced increases in total and cortical blood flows (CBF) to precaptopril levels, increases in PBF were not lowered, suggesting a lesser role for ANG II in PBF responses to ACE inhibition. In experiments performed in conscious, sodium-restricted dogs, Zimmerman et al. (30) found that enalaprilat-induced vasodilation could be attenuated by the administration of both saralasin and B-5630, a BK antagonist, indicating that both the reduction in ANG II formation as well as increases in BK levels were responsible for these responses in the kidney. In concert with these findings, Heller et al. (11) showed in sodium-restricted dogs, but not in those on a normal-salt diet, that BK antagonism attenuates the increase in RBF after ramiprilat by 20%, indicating a role for BK in the RBF responses to ACE inhibition in dogs subjected to sodium restriction.

Attempts to study regional hemodynamic responses in the kidney have been hindered by the inaccessibility of the medullary circulation to direct measurement techniques (10, 15, 29, 39). Many of the previous techniques are either highly indirect or invasive, sometimes requiring the removal of the ureter to access the medullary tissue (21). The recent development of laser-Doppler flowmetry (LDF) with single-fiber needle probes has provided a direct method of dynamic monitoring of renal regional blood flow. These needle probes can be inserted at different depths in the kidney to measure tissue blood flow without discernible tissue damage or impairment of renal function (12–14). The availability of highly potent, selective, and noncompetitive antagonists for the BK B₂ receptor, such as icatibant, formerly known as HOE-140 (19, 26), has allowed a reevaluation of the relative roles of ANG II and BK in the control of renal regional hemodynamics.

This study was designed to evaluate and compare the relative contributions of ANG II and BK to the medullary vasodilatory responses to ACE inhibition in dogs. As shown in the studies mentioned above (11, 30), the relative contributions of ANG II and BK might depend on the dietary sodium intake, which alters the activity level of the renin-angiotensin and the kallikrein-kinin systems. Experiments were therefore conducted in dogs maintained on normal- and low-salt diets.

METHODS

Experiments were conducted on 28 mongrel dogs, weighing between 18 and 20 kg. The dogs were divided into 2 groups:
Renal denervation was performed by cutting all visible nerves projecting to the kidney from the aorticorenal ganglion. The rationale for renal denervation was to minimize the possible effects of altered sympathetic input to the kidney due to changes in arterial baroreceptor activity following ACE inhibitor-induced changes in arterial pressure. The ureter was cannulated for the collection of urine samples. RBF was measured with an electromagnetic flow probe placed around the renal artery and connected to a square-wave flowmeter (Carolina Medical Electronics, Kings, NC). The zero flow was obtained at the beginning and the end of the experiment. Positive-pressure ventilation was provided via a cuffed endotracheal tube with an artificial respirator at a rate of 18 strokes/min and a stroke volume of 15 ml/kg body wt. Body temperature was maintained within the range of 99–101°F using an electric heating pad. Mean arterial pressure was measured from a catheter placed in the abdominal aorta inserted via the right femoral artery and recorded on a polygraph (model 7D; Grass Instruments, Quincy, MA). The left femoral artery was cannulated for the collection of blood samples. The femoral and jugular veins were cannulated for the administration of drugs, infusion of saline and inulin solutions, and additional doses of anesthesia as needed.

The left kidney was exposed through a flank incision, and the renal artery was separated from the surrounding tissue. Renal denervation was performed by cutting all visible nerves projecting to the kidney from the aorticorenal ganglion. The rationale for renal denervation was to minimize the possible effects of altered sympathetic input to the kidney due to changes in arterial baroreceptor activity following ACE inhibitor-induced changes in arterial pressure. The ureter was cannulated for the collection of urine samples. RBF was measured with an electromagnetic flow probe placed around the renal artery and connected to a square-wave flowmeter (Carolina Medical Electronics, Kings, NC). The zero flow was obtained at the beginning and the end of the experiment by momentarily occluding the renal artery. A curved 23-gauge needle cannula was inserted in the renal artery and connected to a pressure transducer to measure renal arterial pressure (RAP). A catheter connected to this needle cannula was used for the direct renal infusion of drug solutions and heparinized saline at the rate of 0.4 ml/min.

A dual-channel laser-Doppler flowmeter (Periflux 4001; Perimed, Stockholm, Sweden) with two needle probes (500-µm diameter) was used to measure relative changes in blood flows in the renal cortex and medulla (12–14). The cortical probe was inserted to a depth of 5 mm into the kidney to position the tip in the midcortical region; the medullary probe was inserted to a depth of ~15 mm, with the tip resting at the junction of the inner and outer medulla. At the end of each experiment, the position of the tips of the needle probes was confirmed by dissecting the kidney and locating the needle tracts. The flow probes were calibrated with a motility standard of a colloidal suspension of latex particles (10-µm microspheres). Brownian motion of the latex particles provides the standard value of 250 perfusion units (PU), with 1 PU being an arbitrary value corresponding to an analog output of 10 mV. The data are reported as percent of the basal levels recorded during the control periods, although the absolute PU values were also monitored and recorded. The basal PU values recorded from the probe placed in the cortical tissue were observed to always be substantially greater (~342 ± 26 vs. ~141 ± 32 PU, n = 7) than those from the medullary probe, indicating the predictable differences in absolute blood flows between both regions (12, 14). The zero flow recordings of the LDF probes were determined by occluding the renal artery momentarily at the beginning and the end of each experiment. To avoid respiratory movement artifacts in the recording of LDF signals, the kidney was maintained in a fixed position by placing it on a plastic holder similar to that used for micropuncture studies. There were no changes in the basal RBF due to such fixation.

After the completion of surgery, a 2.5% solution of inulin in normal saline was administered into the jugular vein for at least 45 min before the beginning of the experimental protocol.
An initial dose of 1.6 ml/kg body wt was followed by a continuous infusion of 0.03 ml min⁻¹·kg body wt⁻¹. The experimental period was started with urine collections for two consecutive 10-min control periods, with an arterial blood sample (2 ml) taken at the midpoint of each collection period. After the control periods, the protocol was continued as follows: each of the 2 groups of dogs (group 1: normal-salt diet, group 2: low-salt diet) were further divided into two subgroups (groups 1A, 1B, 2A, and 2B) with treatments as follows.

The first subgroups of dogs (groups 1A and 2A, n = 7 each) received an intravenous bolus of the BK B₂ receptor blocker icatibant (100–300 µg) first. This dose was effective in blocking the RBF responses to 50 ng of BK (before icatibant: 1.93 ± 0.4 ml min⁻¹·g⁻¹; after icatibant: 0.03 ± 0.001 ml min⁻¹·g⁻¹, n = 12). After a 10-min stabilization period, two 10-min clearances then ensued. These clearances were followed by an intrarenal arterial infusion of the ACE inhibitor enalaprilat (33 µg·kg⁻¹·min⁻¹), and, after 10 min, another two 10-min urine samples were collected.

In the second subgroup of dogs (groups 1B and 2B, n = 7 each), the experimental protocol was carried out as above except for the order of drug administration: enalaprilat was administered first after the control period and icatibant was given after enalaprilat treatment. At the end of each experiment, the electromagnetic flow probe was calibrated in situ by timed collections of blood samples at different flows from a catheter placed in the renal artery into a graduated cylinder. The kidney was then removed, stripped of all surrounding tissue, blotted dry, and weighed so that the calculated parameters could be expressed per gram of kidney weight. Flame photometry (Instrumentation Laboratory, Watertown, MA) was used to determine the sodium and potassium concentrations in plasma and urine. Inulin concentrations in the samples were determined by the anthrone colorimetric technique (Gilford Instruments, Oberlin, OH).

Values are reported as means ± SE. Statistical comparisons of differences in the responses were conducted with the use of ANOVA, followed by the Newman-Keuls test. Differences in the mean values were deemed significant at P ≤ 0.05.

RESULTS

Responses observed in dogs fed a normal-salt diet. Figures 1–3 summarize the RBF, CBF, and MBF responses to enalaprilat and icatibant.

As shown in Fig. 1A, intrarenal ACE inhibition with enalaprilat resulted in a significant increase in RBF (4.9 ± 0.5 to 7.1 ± 0.2 ml min⁻¹·g⁻¹, P ≤ 0.0001). Icatibant administration after ACE inhibition did not affect the observed vasodilation (7.3 ± 0.3 ml min⁻¹·g⁻¹). In Fig. 1B, icatibant administration before ACE inhibition did not cause any changes in RBF nor alter the responses to enalaprilat (4.6 ± 0.5 to 5.9 ± 0.6 ml min⁻¹·g⁻¹, P ≤ 0.0001).

As shown in Fig. 2, the responses observed in CBF were similar to the total RBF responses. ACE inhibition by enalaprilat significantly increased CBF by 23 ± 2% (P = 0.02, n = 6, Fig. 2A). Icatibant treatment following ACE inhibition did not alter the ACE inhibition-induced CBF responses (15 ± 4%). Pretreatment with icatibant (Fig. 2B) did not affect the CBF vasodilatory responses to enalaprilat (11 ± 4%).

Figure 3 shows the MBF responses to ACE inhibition before and after icatibant administration. ACE inhibition resulted in an increase of 33 ± 9% (Fig. 3A, P ≤ 0.01), which was not significantly altered by icatibant administration (29 ± 9%). As shown in Fig. 3B, after

### Table 1. Renal function responses to ACE inhibition before B₂ receptor blockade in dogs fed a normal diet

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Enalaprilat</th>
<th>Icatibant</th>
</tr>
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<tbody>
<tr>
<td>RAP, mmHg</td>
<td>129 ± 5</td>
<td>105 ± 6*</td>
<td>110 ± 5*</td>
</tr>
<tr>
<td>RVR, mmHg·ml⁻¹·min⁻¹·g⁻¹</td>
<td>27.5 ± 3.8</td>
<td>14.7 ± 1.0*</td>
<td>14.0 ± 1.0*</td>
</tr>
<tr>
<td>GFR, ml min⁻¹·g⁻¹</td>
<td>0.84 ± 0.09</td>
<td>0.90 ± 0.09</td>
<td>0.95 ± 0.09</td>
</tr>
<tr>
<td>UV, µl·min⁻¹·g⁻¹</td>
<td>9.5 ± 2.5</td>
<td>11.9 ± 3.5</td>
<td>12.6 ± 3.7</td>
</tr>
<tr>
<td>UₙaV, µmol·min⁻¹·g⁻¹</td>
<td>1.4 ± 0.3</td>
<td>1.6 ± 0.4</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td>FENa, %</td>
<td>1.4 ± 0.4</td>
<td>1.5 ± 0.6</td>
<td>1.4 ± 0.6</td>
</tr>
</tbody>
</table>

Values are means ± SE. ACE, angiotensin-converting enzyme; RAP, renal arterial pressure; RVR, renal vascular resistance; GFR, glomerular filtration rate; UV, urine flow; UₙaV, urinary excretion of sodium; FENa, fractional excretion of sodium. *P < 0.05 compared with control.

### Table 2. Renal function responses to ACE inhibition after B₂ receptor blockade in dogs fed a normal diet

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Icatibant</th>
<th>Enalaprilat</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP, mmHg</td>
<td>120 ± 4</td>
<td>118 ± 5</td>
<td>112 ± 6*†</td>
</tr>
<tr>
<td>RVR, mmHg·ml⁻¹·min⁻¹·g⁻¹</td>
<td>31.7 ± 4.5</td>
<td>30.3 ± 4.6</td>
<td>20.2 ± 3.2*†</td>
</tr>
<tr>
<td>GFR, ml min⁻¹·g⁻¹</td>
<td>0.77 ± 0.09</td>
<td>0.70 ± 0.07</td>
<td>0.66 ± 0.06</td>
</tr>
<tr>
<td>UV, µl·min⁻¹·g⁻¹</td>
<td>12.6 ± 5.6</td>
<td>9.8 ± 3.4</td>
<td>8.2 ± 2.0</td>
</tr>
<tr>
<td>UₙaV, µmol·min⁻¹·g⁻¹</td>
<td>1.5 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>FENa, %</td>
<td>1.4 ± 0.7</td>
<td>1.9 ± 0.4</td>
<td>1.7 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. control; †P < 0.05 vs. icatibant.
pretreatment with icatibant, the increases in MBF in response to ACE inhibition averaged $17 \pm 2\%$ ($P \leq 0.01$), which was significantly less than the response when the ACE inhibition was given first. Also, the MBF responses to ACE inhibition ($33 \pm 9\%$) were significantly greater than those of CBF ($23 \pm 2\%, P \leq 0.002$).

Tables 1 and 2 summarize the results in RAP, renal vascular resistance (RVR), glomerular filtration rate (GFR), urine flow (UV), and sodium excretion ($U_{\text{Na}}V$) in dogs fed a normal-salt diet. Table 1 shows the results when the ACE inhibitor was administered before $B_2$ receptor blockade. ACE inhibition significantly decreased RAP and RVR, and icatibant did not reverse these responses. GFR, UV, $U_{\text{Na}}V$, and fractional excretion of sodium ($F\text{E}_{\text{Na}}$) were not significantly altered by enalaprilat.

As shown in Table 2, pretreatment with icatibant did not prevent the decreases in RVR in response to ACE inhibition, but the relative decrease in RVR was only 36% compared with the 47% decrease when enalaprilat was administered first.

Responses observed in low-salt diet dogs. Figures 4–6 depict the results observed in dogs fed 0.01% salt for 5 days. Figure 4A shows the total RBF responses. ACE inhibition resulted in significant increases in RBF ($4.4 \pm 0.3$ to $5.6 \pm 0.4$ ml·min$^{-1}$·g$^{-1}$, $P \leq 0.008$), as observed in the normal-salt dogs. Icatibant administration after ACE inhibition did not significantly alter these RBF responses. However, when icatibant was administered before enalaprilat, the increases in RBF were prevented as shown in Fig. 4B. Likewise, CBF significantly increased with ACE inhibition (Fig. 5A; $28 \pm 10\%$, $P \leq 0.02$), and these responses were not altered by subsequent administration of icatibant ($25 \pm 10\%$). As depicted in Fig. 5B, however, icatibant before ACE inhibition prevented the previously observed cortical vasodilatory responses.

MBF responded in the same pattern as RBF and CBF (Fig. 6). As shown in Fig. 6A, ACE inhibition resulted in a significant increase in MBF ($24 \pm 9\%$, $P \leq 0.005$), and there was a slight further increase that was not statistically significant after icatibant administration ($30 \pm 7\%$). As seen in Fig. 6B, icatibant before ACE inhibition markedly and significantly reduced the medullary vasodilation with ACE inhibition.

Tables 3 and 4 show the RAP, RVR, GFR, UV, $U_{\text{Na}}V$, and $F\text{E}_{\text{Na}}$ responses to ACE inhibition when $B_2$ receptors are blocked before and after enalaprilat administration. ACE inhibition decreased both RAP and RVR, and icatibant did not reverse these responses. The other parameters were not significantly altered by any of the treatments. Although the overall changes in UV were not significant, we did observe an ACE inhibition-induced diuresis in 4 dogs. In the rest of the dogs, the ACE inhibitor, although administered intrarenally, still lowered systemic pressure, and this resulted in an antidiuresis. The variability between dogs could have masked any overall statistical significance. As shown in Table 4, icatibant pretreatment did not have a significant effect on the previously observed responses to ACE inhibition.
DISCUSSION

In dogs fed a normal salt diet, ACE inhibition resulted in increases in medullary, cortical, and total renal blood flows, as have been reported by other investigators (1, 4, 16). These responses were not altered significantly by icatibant administration either before or after enalaprilat treatment. The observed responses in medullary blood flow were significantly larger than those of CBF, indicating a greater sensitivity of medullary circulation to ACE inhibition. These results suggest that in conditions of normal salt intake, the observed blood flow changes due to ACE inhibition are less sensitive to kinin antagonism and may therefore be dependent mainly on diminished intrarenal ANG II formation rates.

A low-salt diet has been reported to upregulate the activity of both the renin-angiotensin and the kallikrein-kinin systems (23, 24). As indicated by the decreased urinary and fractional excretion of sodium compared with those of normal-salt diet dogs (Tables 1-4), 0.01% salt feeding for 5 days was effective in stimulating renal sodium conservation. In these animals, ACE inhibition also resulted in increases in cortical, medullary, and total renal blood flows. B2 receptor blockade following ACE inhibition did not significantly influence the observed responses. Interestingly, when blockade of B2 receptors was imposed before ACE inhibition, there was a loss of medullary, cortical, and total renal blood flow vasodilation in response to intrarenal enalaprilat infusion. Under low-salt conditions, therefore, the observed enalaprilat-induced renal vasodilation is highly sensitive to kinin antagonism. This suggests that ACE inhibition in sodium-restricted dogs substantially augments intrarenal kinin formation, which in turn is responsible for much of the increases in medullary and cortical blood flows. In both cases the relative medullary responses are observed to be greater than those of CBF, implying a greater sensitivity of medullary circulation to ACE inhibition. This greater sensitivity could be attributable to the reportedly higher ANG II concentrations and receptor density in the medulla than in the cortex (22).

Previous reports (12) have shown that in response to an intra-arterial bolus administration of ANG II, medullary blood flow responses were greater than those observed in the cortex, indicating a greater sensitivity of the medullary circulation to ANG II. Additionally, vasoactive modulators such as BK and nitric oxide are different in the medulla (28, 31), leading to differential sensitivities.

The dependence of the vasodilatory responses to ACE inhibition on kinin B2 receptors under conditions of stimulated renin-angiotensin system activity demonstrates an augmented paracrine role for kinins in the regulation of intrarenal regional hemodynamics in this condition. Possible explanations include a shift or difference in relative activation or dependence of renal vasculature on ANG II and BK levels and/or receptors. A surprising finding, however, not consistent with the explanation, is that in the low-sodium diet dogs, icatibant did not reverse the vasodilatory effects of ACE inhibition, despite its ability to prevent them. It seems possible that the augmented intrarenal kinin levels due to ACE inhibition initiates a vasodilatory signal transduction cascade that, once activated, is not easily reversed or arrested by subsequent blockade of the B2 receptor with a receptor antagonist. In contrast, icatibant administration before ACE inhibition would be expected to bind the B2 receptors, making them unreceptor

Table 4. Renal function responses to ACE inhibition after B2 receptor blockade in dogs fed a low-salt diet

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Icatibant</th>
<th>Enalaprilat</th>
</tr>
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<tbody>
<tr>
<td>RAP, mmHg</td>
<td>142 ± 5</td>
<td>126 ± 8</td>
<td>129 ± 6</td>
</tr>
<tr>
<td>RVR, mmHg·ml⁻¹·min⁻¹</td>
<td>33.1 ± 3</td>
<td>23.2 ± 2.8</td>
<td>22.8 ± 2.2</td>
</tr>
<tr>
<td>GFR, ml·min⁻¹·g⁻¹</td>
<td>0.78 ± 0.08</td>
<td>0.70 ± 0.03</td>
<td>0.76 ± 0.07</td>
</tr>
<tr>
<td>UV, µl·min⁻¹·g⁻¹</td>
<td>19.0 ± 10.2</td>
<td>7.3 ± 0.8</td>
<td>11.1 ± 3.9</td>
</tr>
<tr>
<td>UαV, µmol·min⁻¹·g⁻¹</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>FEα, %</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>RVR, mmHg·ml⁻¹·min⁻¹</td>
<td>44.9 ± 10.2</td>
<td>44.4 ± 11.3</td>
<td>35.8 ± 8.7†</td>
</tr>
<tr>
<td>GFR, ml·min⁻¹·g⁻¹</td>
<td>0.66 ± 0.13</td>
<td>0.55 ± 0.11</td>
<td>0.57 ± 0.13</td>
</tr>
<tr>
<td>UV, µl·min⁻¹·g⁻¹</td>
<td>3.4 ± 5.6</td>
<td>5.1 ± 1.7</td>
<td>5.0 ± 1.6</td>
</tr>
<tr>
<td>UαV, µmol·min⁻¹·g⁻¹</td>
<td>0.09 ± 0.04</td>
<td>0.10 ± 0.05</td>
<td>0.09 ± 0.05</td>
</tr>
<tr>
<td>FEα, %</td>
<td>0.12 ± 0.06</td>
<td>0.15 ± 0.06</td>
<td>0.12 ± 0.06</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. control; †P < 0.05 vs. icatibant.
responsive to elevated kinin concentrations caused by ACE inhibition and hence its ability to prevent the effects of ACE inhibition. Another possible explanation is the activation of BK B_1 receptors, which have been reported to be present in canine kidneys (17, 20, 25). The B_2 receptors would become activated when excess availability of BK leads to the formation of des-Arg^9-BK, its primary ligand (27). These possibilities, however, remain to be investigated. Catinat alone did not alter any of the measured renal parameters in either group of dogs. This observation, especially in the low-salt diet dogs, was unexpected and would suggest that although increased kinin levels may play a significant role during ACE inhibition, kinins exert a minimal effect on blood flow when ACE is intact. This may be due to the high affinity that ACE has for BK (catalytic rate constant/Michaelis-Menten constant = 3.900–5.000 s^{-1} M^{-1}) during control levels, which maintains BK at low levels (5). During ACE inhibition, however, BK levels would be increased to a greater extent, thereby allowing physiological responses to blockade of B_2 receptors. Our findings are consistent with other reports (11, 16, 30) that administration of a BK receptor blocker does not decrease blood flow nor increase resistance in control conditions.

In conclusion, the present investigation suggests that under normal salt intake, B_2 receptor blockade does not significantly alter the renal vasodilatory responses to ACE inhibition in both the renal medulla and the cortex, indicating that under these conditions of normal salt intake, enhanced BK levels do not exert a major influence on regional renal hemodynamics. Under low sodium intake on the other hand, B_2 receptor blockade prevents the vasodilatory responses to the same dose of ACE inhibition, suggesting a major role for enhanced BK levels and the stimulation of B_2 receptors following ACE inhibition. The greater responses by medullary circulation compared with the cortical circulation indicate that this region of the kidney may have a greater sensitivity to the changes in intrarenal levels of ANG II and BK caused by ACE inhibition.

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