Differential effects of ACE and AT₁ receptor inhibition on chemoattractant and adhesion molecule synthesis

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Morrissey, Jeremiah J., and Saulo Klahr. Differential effects of ACE and AT₁ receptor inhibition on chemoattractant and adhesion molecule synthesis. Am. J. Physiol. 274 (Renal Physiol. 43): F580–F586, 1998.—Ureteral obstruction causes infiltration of the kidney by monocytes/macrophages. This infiltrate is significantly reduced by administration of an angiotensin-converting enzyme (ACE) inhibitor but not by a specific angiotensin II type 1 receptor (AT₁ receptor) antagonist. Chemoattractants and cell surface adhesive molecules mediate monocyte/macrophage infiltration. Rats with unilateral ureteral obstruction (UUO) of 1, 3, or 5 days duration were untreated or given enalapril or SC-51316 in the drinking water. We measured the mRNA levels of monocyte chemoattractant peptide 1 (MCP-1), a chemoattractant, and levels of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), two cell surface adhesion proteins. MCP-1 mRNA increased significantly after 1 day of UUO and increased further through 5 days of UUO in the obstructed kidney. ICAM-1 mRNA also increased significantly after 1 day but steadily declined through 5 days of UUO in the obstructed kidney. VCAM-1 mRNA did not increase significantly until after 3 days of UUO and increased further through 5 days of obstruction. Enalapril or SC-51316 treatment had no significant effect on ICAM-1 mRNA levels. MCP-1 mRNA levels were reduced but remained significantly elevated. Enalapril significantly blunted the increase in VCAM-1 mRNA levels and VCAM-1 protein determined by immunocytochemistry; SC-51316 had no significant effect. Thus changes in VCAM-1 mRNA levels may account for the differential effect of enalapril and SC-51316 on monocyte/macrophage infiltration of the kidney during ureteral obstruction.


THE PRODUCTION OF CHEMOATRACTANTS AGENTS WITHIN AN INJURED TISSUE AND THE DEVELOPMENT OF ADHESIVE PROPERTIES BY MONOCYTES AND ENDOTHELIUM OVERLYING IT RESULTS IN INFILTRATION OF THAT TISSUE BY CIRCULATING MONOCYTES (2). SEVERAL CHEMOATTRACTANTS ARE PRODUCED BY THE KIDNEY DURING UUO (4, 5, 27); HOWEVER, LITTLE IS KNOWN ABOUT THE PRODUCTION OF ADHESIVE PROTEINS WITHIN THE KIDNEY DURING UUO (26). IN SEVERAL EXPERIMENTAL RENAL DISEASES AND IN NEPHROPATHIES IN HUMANS, THE ADHESION MOLECULES [INTERCELLULAR ADHESION MOLECULE 1 (ICAM-1) AND VASCULAR CELL ADHESION MOLECULE 1 (VCAM-1)] ARE THOUGHT TO BE IMPORTANT IN ENDOTHELIAL ADHESION AND MIGRATION OF LEUKOCYTES, INCLUDING MONOCYTES, INTO TISSUES (2, 3). ADMINISTRATION OF MONOClonAL ANTIBodies, WHICH BLOCK ICAM-1 TO ANIMALS WITH EITHER ISCHEMIC RENAL INJURY (12) OR NEPHROTOXIC NEPHRITIS (21), REDUCES BUT NOT TOTALLY ELIMINATES SUBSEQUENT KIDNEY DAMAGE.

In the present in vivo investigation, we examined the effects of UUO on the expression of mRNA for the adhesion molecules ICAM-1 and VCAM-1 and the chemoattractant, monocyte chemoattractant protein 1 (MCP-1). In addition, we determined how the mRNA expression of these molecules was affected by the administration of an ACE inhibitor or an AT₁ receptor blockade.

METHODS

Animals and experimental protocols. Female Sprague-Dawley rats (Harlan Bioproducts, Indianapolis, IN) weighing 180–230 g were used in these experiments, which employed protocols approved by the Animal Care Committee of Barnes-Jewish Hospital (St. Louis, MO). Most of the rats underwent UUO, as described previously (9, 11, 18). Control rats (n = 4), also referred to as normal rats, had no surgical manipulation. All animals were fed a standard rat chow and given tap water or tap water containing ACE inhibitor or AT₁ receptor antagonist ad libitum. Rats were killed after 1, 3, or 5 days of UUO (12 rats at each time point) under pentobarbital sodium anesthesia (5.0 mg/kg body wt ip). The four animals with UUO that comprised each experimental group were untreated or given the ACE inhibitor enalapril (200 mg/l) or the AT₁ receptor antagonist SC-51316 (20 mg/l) in the drinking water 1 day prior to and throughout UUO.

RNA extraction. For RNA extraction, kidneys from each group were perfused in situ with cold Hanks’ balanced salt solution. The cortex was dissected immediately and minced in...
Ultraspec RNA Reagent (Biotex Laboratories, Houston, TX).
In another group of four animals that had sustained UUO for 5 days but were not treated, the cortex was processed by sieving and separated into glomeruli and tubules (11) prior to preparation of total RNA. Total RNA was extracted, dissolved in RNase-free water (Sigma, St. Louis, MO), and quantitated by ultraviolet (UV) spectrophotometry at 260 and 280 nm.

Characterization and relative quantitation of MCP-1, ICAM-1, and VCAM-1 mRNA by RT-PCR. Oligo(dT)-primed first-strand cDNA was synthesized with cDNA cycle kit from Promega (Madison, WI) using 2 µg of total RNA. The mixture of total RNA (2 µg/10 µl RNase-free water) and oligo(dT) (1 µl) was incubated at 65°C for 10 min to denature the secondary structure, then chilled on ice immediately for 5 min. After 5 units of avian myeloblastic virus transcriptase was added, the resulting mixture was incubated at 42°C for 1 h, then heated to 94°C for 5 min, and chilled on ice. A second round of reverse transcription was performed after adding 5 units of enzyme.

PCR was performed, using 3 µl of each cDNA incubation. Amplification was done in a total volume of 50 µl containing PCR buffer [50 mM KCl, 10 mM Tris- HCl, 1.5 mM MgCl2, 200 µM of each dNTP, 50 pmol of oligonucleotide primers, and 1/25 unit of Taq DNA polymerase (Promega)]. To quantitate PCR products and to confirm the integrity of the RNase, we amplified a housekeeping gene, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in companion tubes. We used a small amount (1 µl) of cDNA from the kidney cortex with 25 pmol of primers to amplify the GAPDH message. The MCP-1 primers were designed from the sequence of the rat gene: 5’ (RATMCP1) ATGCAGGTCTCTGTAAG (sense) and 5’ CTCT-

TGAGACACCTTCATTTAGG (antisense) to yield a 256-bp product. The ICAM-1 primers were designed from the sequence of the rat gene: 5’ (RATICAM) TTGGAGACTAACTG-

GATGAA (sense) and 5’ TGATCTTCTCGGCGGTA (antisense) to yield a 1,396-bp product. The VCAM-1 primers were designed from the sequence of the rat gene: 5’ (RNVCAM1R) GGAGACACTGCTACATCTCCTGG (sense) and 5’ TCCT-

TCATGTTGGCTTTTCTTGC (antisense) to yield a 336-bp product. The GAPDH primers were designed from the sequence of the rat gene: 5’ (RATGAPDHA) AATGCATCCTGCA-

TTGACCCATTCCTTATTGG (antisense) and 5’ GTAGCCATATTCATTGTCATA (antisense) to yield a 100-bp product. PCR products were analyzed as described previously (9–11). After amplification, 15 µl of each PCR reaction mixture were electrophoresed through a 1.2% agarose gel with ethidium bromide (0.5 µg/ml). The gel was photographed with Polaroid type 665 positive/negative film (Polaroid, Cambridge, MA) over UV light at the same exposure and development time for all gels photographed. The bands on the negative film were scanned by densitometry (Sepra Scan 2000i software; Integrated Separation Systems, Natwick, MA) for relative quantitation. The PCR products of MCP-1 and GAPDH, ICAM-1 and GAPDH, or VCAM-1 and GAPDH (those amplified from the same cDNA) were electrophoresed in the same gel, and ratios for MCP-1/GAPDH, ICAM-1/GAPDH, or VCAM-1/GAPDH were determined to eliminate gel-to-gel or film-to-film variance.

Immunocytochemical localization of VCAM-1. At the time of death of rats, the kidneys were perfused in situ with ice-cold Histochoice (Amresco, Solon, OH) after perfusion in the balanced salt solution (9–11). Coronal sections of each kidney were embedded in the same paraffin block, and 4-µm sections were prepared. The deparaffinized and rehydrated sections were treated with an anti-VCAM-1 polyclonal antibody, SC-1504 (Santa Cruz Biotechnology, Santa Cruz, CA), at a 1:100 dilution overnight at 4°C. The primary antibody was located with a horseradish peroxidase-linked secondary antibody (Sigma) and a 3,3’-diaminobenzidine reaction product. The sections were lightly counterstained with Mayer’s hematoxylin.

RESULTS
Monocyte chemotactic protein 1. After obstruction of the ureter, there is an infiltration of the kidney by monocytes/macrophages (9–11, 30). One compound that contributes in part to monocyte attraction is MCP-1. As shown previously by Diamond et al. (4) and by this study, the mRNA for MCP-1 increased fivefold in the obstructed kidney within 1 day of ureteral obstruction (Fig. 1 and Table 1). The upregulation (P < 0.003) persisted for 5 days of UUO and reached a greater than ninefold increase (P < 0.001). There was no significant change in the amount of MCP-1 mRNA in the contralateral unobstructed kidney of the same rats at any time point (Fig. 1 and Table 1).

Adhesion proteins. Although chemoattractants activate monocytes, it is the increased expression of adhesion proteins, which bind the activated monocytes, that effects the transmigration of these cells into the affected tissue. Thus we also measured the amount of ICAM-1 mRNA during UUO, which had also been investigated by Diamond and co-workers (4). The mRNA for ICAM-1 was relatively abundant in the normal kidney, compared with the mRNA for MCP-1 (see Figs. 1 and 2, showing the results of PCR amplification when

![Fig. 1](http://ajprenal.physiology.org/)
Table 1. Relative levels of mRNA for MCP-1, ICAM-1, and VCAM-1 in normal kidney and kidney with unilateral ureteral obstruction

<table>
<thead>
<tr>
<th>Condition</th>
<th>MCP-1 mRNA</th>
<th>ICAM-1 mRNA</th>
<th>VCAM-1 mRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal kidneys</td>
<td>13 ± 8</td>
<td>105 ± 16</td>
<td>50 ± 8</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>19 ± 8</td>
<td>223 ± 76</td>
<td>34 ± 16</td>
</tr>
<tr>
<td>Obstructed</td>
<td>64 ± 16*</td>
<td>388 ± 140†</td>
<td>38 ± 8</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>16 ± 8</td>
<td>171 ± 46</td>
<td>20 ± 45§</td>
</tr>
<tr>
<td>Obstructed</td>
<td>76 ± 26†</td>
<td>243 ± 125$</td>
<td>81 ± 169</td>
</tr>
<tr>
<td>Day 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>19 ± 8</td>
<td>12 ± 4*</td>
<td>11 ± 6$</td>
</tr>
<tr>
<td>Obstructed</td>
<td>120 ± 18‖</td>
<td>122 ± 34</td>
<td>121 ± 24†</td>
</tr>
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</table>

Values are means ± SD in 4 separate animals of relative amount of each mRNA normalized to the amount of glyceraldehyde-3-phosphate dehydrogenase mRNA. MCP-1, monocyte chemotactic protein 1; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1.*P < 0.003 vs. normal. †P < 0.003 vs. normal. ‡P < 0.001 vs. normal. §P < 0.02 vs. normal.

Each product was amplified the same number of cycles. As with MCP-1 mRNA, there was a significant 3.7-fold increase in ICAM-1 mRNA in the obstructed kidney, compared with the normal kidney after 1 day of UUO (Fig. 2 and Table 1). In contrast to MCP-1 mRNA levels in the contralateral unobstructed kidney, which did not change, ICAM-1 mRNA in the unobstructed contralateral kidney doubled (P < 0.03) after 1 day of UUO (Fig. 2 and Table 1). Also dissimilar to results with MCP-1 mRNA, there was a decline in the amount of ICAM-1 mRNA in the obstructed kidney by days 3 and 5 of UUO. Interestingly, the amount of ICAM-1 mRNA in the contralateral kidney fell significantly below the level seen in the normal kidney (P < 0.003) by day 5 of UUO (Fig. 2 and Table 1).

Another cell adhesion molecule that binds monocytes is VCAM-1 (2, 5). In contrast to MCP-1 and ICAM-1 mRNA, the mRNA for VCAM-1 did not change after 1 day of UUO (Fig. 3 and Table 1). After 3 days of UUO, the amount of VCAM-1 mRNA was modestly but significantly increased 1.6-fold (P < 0.02) in the obstructed kidney, compared with levels in the normal kidney. The mRNA for VCAM-1 increased further to 2.4-fold that of the normal kidney by 5 days of UUO. In the unobstructed contralateral kidney, VCAM-1 mRNA significantly declined from normal levels at days 3 (P < 0.02) and 5 (P < 0.02) of UUO.

Renal site of chemoattractant and adhesion molecule activation. During UUO, the tubulointerstitium of the kidney is infiltrated by monocytes/macrophages, whereas, in the glomeruli, there is an actual decrease in the number of these lymphohematopoietic cells (18, 30). The glomeruli of the kidney with UUO are histologically indistinguishable from those of the normal kidney or the glomeruli of the contralateral unobstructed kidney through at least day 5 of UUO (9). We therefore separated glomeruli from tubules, using established techniques, and determined the relative level of mRNA expression of the chemoattractant MCP-1 and the adhesion protein VCAM-1 (Fig. 4). Because the ICAM-1 mRNA level fell by day 5 in the ureteral obstructed kidney, we did not perform this analysis for ICAM-1 mRNA. The mRNA for GAPDH was indistinguishable when comparing glomeruli or tubules prepared from the kidney with an obstructed ureter with those from the contralateral unobstructed kidney. Similarly, the relative amount of VCAM-1 mRNA or MCP-1 mRNA was not demonstrably different between the two different groups of glomeruli (Fig. 4). In contrast, tubules isolated from kidneys with an obstructed ureter displayed significant and dramatic increases in both VCAM and MCP-1 mRNA, compared with tubules isolated from the contralateral unobstructed kidneys (Fig. 4).

Effect of ACE and AT1 receptor inhibition. Rats with UUO treated with an ACE inhibitor had a significant
reduction in monocyte/macrophage infiltration and fibrosis of the obstructed kidney (9–11, 18). Interestingly, rats treated with an antagonist of the AT₁ receptor had a significant reduction in fibrosis but not a significant change in the number of infiltrating monocytes/macrophages in the obstructed kidney (9). We therefore measured the amounts of mRNA for MCP-1, ICAM-1, and VCAM-1 to determine whether treatment with ACE inhibitor or AT₁ receptor antagonists at the doses used in the previous study (9) differentially affect chemotraction and adhesion. Rats with UUO were given enalapril or the AT₁ receptor antagonist SC-51316 for 5 days, and the levels of mRNA for the adhesion molecules and MCP-1 were determined.

After 5 days of UUO, there were significant 35 (P < 0.006) and 41% (P < 0.003) decreases in the mRNA for MCP-1 in the obstructed kidney of animals given enalapril or SC-51316, respectively, compared with the obstructed kidney of untreated rats with UUO. The overall amount of MCP-1 mRNA in treated animals with UUO, however, remained 5.5- to 6-fold increased over normal levels (Fig. 1 and Table 1 vs. Table 2). The amount of ICAM-1 mRNA in the obstructed kidney was not significantly different among rats with UUO that were untreated or treated with an ACE inhibitor or the AT₁ antagonist SC-51316 (Fig. 2, Table 2). The amount of VCAM-1 mRNA, on the other hand, was decreased in the obstructed kidney (P < 0.001) of rats with UUO receiving an ACE inhibitor, compared with the obstructed kidney of untreated rats, and was indistinguishable from the levels found in the kidney of normal animals (Fig. 3 and Table 1). The amount of VCAM-1 mRNA in the obstructed kidney of rats with UUO treated with SC-51316 was not different from that of the obstructed kidney of untreated rats (Table 2). Although treatment with ACE inhibitor or the AT₁ receptor antagonist increased VCAM-1 mRNA levels in the contralateral unobstructed kidney, these increases were not significant (P < 0.07 and P < 0.12, respectively).

Renal site of VCAM-1 expression. Both MCP-1 (4) and ICAM-1 (26) have been immunolocalized in the ureteral obstructed kidney. We therefore concentrated on the immunolocalization of VCAM-1. Figure 5A is a histological section from the 5-day ureteral obstructed kidney prepared with no primary antibody. Figure 5B is a histological section obtained from the kidney of a normal rat and shows VCAM-1 expression on the basal membrane of some but not all cells of a particular tubule. In addition, there is weak expression of VCAM-1 on the parietal epithelial cells of Bowman’s capsule. In sections obtained from the contralateral unobstructed kidney of rats with UUO for 5 days, the VCAM-1 expression likewise occurred in occasional cells of each tubule cross section (Fig. 5C). In addition, the staining of Bowman’s capsule was less evident (compare Fig. 5, B and C). Sections of the kidney with unilateral obstruction of 5 days duration had increased expression of VCAM-1 in most of the tubular epithelial cells (Fig. 5D). This increased expression of VCAM-1 was displayed uniformly among all cells of the affected tubules and was not confined to the basal surfaces (Fig. 5D). In addition, cells within the widened interstitium appeared to express VCAM-1 (contrast the density of Fig. 5, A, with that of D). In sections obtained from the obstructed kidney (5 days UUO) of rats treated with the AT₁ receptor antagonist (Fig. 5E), VCAM-1 expression in tubules appeared to be similar to that in tubules from the obstructed kidney of untreated rats (Fig. 5D). As reported previously (9), the interstitium was not as

<table>
<thead>
<tr>
<th>Condition</th>
<th>MCP-1 mRNA</th>
<th>ICAM-1 mRNA</th>
<th>VCAM-1 mRNA</th>
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</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>19±8</td>
<td>12±4</td>
<td>11±6</td>
</tr>
<tr>
<td>Contralateral kidney</td>
<td>120±18</td>
<td>122±34</td>
<td>121±24</td>
</tr>
<tr>
<td>Obstructed kidney</td>
<td>21±14</td>
<td>26±6</td>
<td>36±4</td>
</tr>
<tr>
<td>ACE inhibitor treated</td>
<td>78±14*</td>
<td>97±40</td>
<td>52±14*</td>
</tr>
<tr>
<td>Contralateral kidney</td>
<td>13±8</td>
<td>38±8</td>
<td>32±8</td>
</tr>
<tr>
<td>Obstructed kidney</td>
<td>71±20*</td>
<td>143±56</td>
<td>103±26</td>
</tr>
</tbody>
</table>

Values are means ± SD in 4 separate animals of relative amount of each mRNA normalized to amount of GAPDH mRNA. *P < 0.006 vs. untreated obstructed. †P < 0.001 vs. untreated obstructed.
widened in rats treated with receptor antagonist. As noted in the ureteral obstructed kidney of untreated animals (Fig. 5D), VCAM-1 expression was uniformly elevated among all cells of the affected tubules of animals treated with AT1 receptor antagonist (Fig. 5E). In sections obtained from the ureteral obstructed kidney of rats treated with ACE inhibitor, there was a marked reduction in VCAM-1 expression (Fig. 5F). Although fainter, VCAM-1 expression appears to be uniform around the affected tubules in the obstructed kidney obtained from rats treated with enalapril (Fig. 5F), compared with the contralateral kidney of untreated rats (Fig. 5C) or the kidney of normal rats (Fig. 5B). As noted previously, the interstitium is not significantly expanded in animals treated with ACE inhibitor (9, 10).
DISCUSSION

In this investigation, we have shown that there is a differential regulation of the expression of the mRNA for the chemoattractant protein MCP-1 and the adhesion proteins ICAM-1 and VCAM-1 during the development of obstructive nephropathy. The mRNA for MCP-1 was increased by 1 day of UUO and remained elevated for the 5 days of the study. In addition, the amount of MCP-1 mRNA did not change in the contralateral unobstructed kidney. The increased expression of ICAM-1 mRNA was greater at day 1 but thereafter declined through day 5 of UUO. The expression of VCAM-1 mRNA, on the other hand, was not increased until days 3–5 of UUO. Interestingly, the expression of ICAM-1 and VCAM-1 mRNA progressively and significantly declined in the contralateral unobstructed kidney when normalized for the amount of GAPDH mRNA. The reason for this decrease from the basal level of expression in the contralateral kidney for ICAM-1 and VCAM-1 mRNA is not precisely known.

A beneficial component of the effect of ACE inhibition to ameliorate renal disease is the generation of increased nitric oxide levels, presumably by the expected increase in kinin concentration (18). The effect of kinins on overall chemoattractant/adhesion molecule synthesis in the kidney is not known. A systemic increase in kinin levels or an increase in both kidneys could be a factor in the findings reported for the contralateral kidney.

The expression of many proteins involved in a tissue inflammatory process requires the complex interplay of several transcription factors (1). We have found the activity of numerous transcription factors is increased in the kidney with an obstructed ureter (19). Importantly, the activity of some transcription factors is decreased in the contralateral unobstructed kidney from the activity observed in the kidneys of sham-operated animals (19). This could contribute, in part, to a differential effect on MCP-1, ICAM-1, and VCAM-1 mRNA expression. The nuclear factor-κB (NF-κB) family of transcription factors mediates the induction of MCP-1, ICAM-1, and VCAM-1 (1). We have recently found that an ACE inhibitor (20) and angiotensin II receptor antagonists (13) differentially blunt NF-κB activation in the kidney due to ureteral obstruction. Altered regulation of NF-κB isotypes due to ACE inhibition or to AT1 receptor antagonism may also explain the effects we observed on MCP-1, ICAM-1, and VCAM-1 induction. The time course for MCP-1, ICAM-1, and VCAM-1 beyond the 5 days of this study is not known. The present observations are in keeping with the observed time course of monocyte/macrophage infiltration of the kidney during UUO (4, 18, 26, 30).

An important finding of this investigation is that administration of an ACE inhibitor in vivo decreased VCAM-1 mRNA expression in the obstructed kidney to a level indistinguishable from that of normal kidneys. In addition, ACE inhibitor administration abrogated, to a degree, MCP-1 mRNA expression. The combined significant declines in the expression of a chemoattractant and an adhesion protein can account, in part, for the observed decline in monocyte/macrophage infiltration of the renal interstitium of the obstructed kidney compared with that of untreated rats with obstructive nephropathy.

A second important and consistent finding of this investigation is that the molecular and cellular alterations leading to the development and/or progression of monocyte/macrophage infiltration are confined to the tubule compartment of the renal cortex. This observation is in keeping with previous studies demonstrating tubular localization of MCP-1 (4) and osteopontin (5) expression. Glomeruli did not exhibit a change with respect to MCP-1 mRNA or VCAM-1 mRNA levels when normalized for GAPDH mRNA. Glomeruli are not infiltrated by monocytes/macrophages during ureteral obstruction, and, in fact, the few resident monocytes/macrophages are decreased (18, 30). The lack of change in mRNA for the chemoattractant MCP-1 and the adhesion protein VCAM-1 is consonant with these observations.

The immunocytochemical localization of VCAM-1 protein to the basal membrane and to interstitial cells in the ureteral obstructed kidney is in keeping with the role of an adhesion molecule anchoring monocytes/macrophages to the cell surface. Previous studies had immunolocalized the chemoattractant MCP-1 expression to the apical surface of the tubular epithelium (4). The adhesion molecule ICAM-1 was found to be immunolocalized within the interstitium and perivascular adventitia during ureteral obstruction (26). Our immunocytochemical localization of VCAM-1 in the normal kidney, the ureteral obstructed kidney, and the contralateral kidney of the rat is consistent with results of renal biopsy of normal kidneys and those with glomerulonephritis (28).

Treatment with an AT1 receptor antagonist did not decrease VCAM-1 mRNA in the kidney with an obstructed ureter. The amount of MCP-1 mRNA was significantly decreased but still remained significantly elevated compared with normal levels. We had found previously (9) that at this dose of AT1 receptor antagonist the monocyte/macrophage infiltration into the kidney with an obstructed ureter was not abated. The dose of inhibitor, however, did ameliorate subsequent effects of these monocytes/macrophages on the progression of fibrosis of the tubulointerstitium (9). Interestingly, it has recently been reported that expression of the chemokine regulated on activation normal T-expressed and presumably secreted (RANTES) by angiotensin II is mediated by the AT2 and not AT1 receptor (33). The effect of AT2 receptor inhibition on MCP-1 expression is not at present known. Perhaps a higher dose of inhibitor (SC-51316) would blunt VCAM-1 mRNA induction and subsequent monocyte/macrophage infiltration; however, the dose used in this and the previous study is near the maximum water solubility of the compound. The observation of a significant effect on VCAM-1 mRNA induction and on monocyte/macrophage infiltration points to participation of this adhesion molecule in the overall pathophysiology of
obstructive nephropathy and the overall beneficial effect of ACE inhibitors on the progression of renal disease. The differential effects of ACE inhibitors and AT1 receptor antagonists on selectin, integrin, or osteopontin synthesis by the kidney would be other avenues to explore to more fully to appreciate their therapeutic potential.

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