Angiotensin Inhibition Reduces Glomerular Damage and Renal Chemokine Expression in MRL/lpr Mice

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ABSTRACT

Beneficial effects of angiotensin II inhibition during inflammatory renal disease may involve both hemodynamic and nonhemodynamic mechanisms. To analyze whether angiotensin II inhibition has protective effects on lupus-like, autoimmune-mediated renal damage in MRL/lpr mice, four groups of mice were treated orally for 6 weeks with: 1) vehicle, 2) enalapril (3.0 mg/kg per day), 3) candesartan cilexetil (5.0 mg/kg), or 4) amlodipine (10 mg/kg) as a blood pressure control (n = 9–12/group). All antihypertensive treatments lowered blood pressure to a similar level compared with vehicle group (enalapril: 99.8 ± 3.3 mm Hg; candesartan: 101 ± 9 mm Hg; amlodipine: 103.8 ± 6.7 mm Hg; vehicle: 113.5 ± 4.6 mm Hg). Vehicle-treated mice developed a moderate glomerular injury with albuminuria (35.1 ± 39.0 µg/mg of creatinine). Glomerular lesions consisted of immune complex deposition and mesangial expansion with increased mesangial cell proliferation. Amlodipine treatment had no significant protective effects. In contrast to vehicle- and amlodipine-treated mice, those subjected to angiotensin II blockade with enalapril or candesartan had reduced albuminuria, glomerular expansion, and mesangial proliferation. This was associated with significantly reduced renal chemokine mRNA expression compared with vehicle treatment. Our results show that inhibition of angiotensin II has protective effects on the glomerular damage of MRL/lpr mice that extend beyond hemodynamics and involve down-modulation of glomerular inflammation, reduction of mesangial cell proliferation, and decrease in chemokine expression.

The role of the renin-angiotensin system (RAS) in the progression of experimental renal disease (Mackenzie et al., 1994; Wolf et al., 1997; Ruiz-Ortega et al., 1998; Hisada et al., 1999; Satoh et al., 2001) and in patients with various forms of renal disease (Ravid et al., 1993; Burnier and Brunner, 2000) is well established. Increased expression of mRNA for components of the RAS [renin, angiotensin converting enzyme (ACE), and angiotensinogen] has been shown in kidneys of nephritic and hypertensive patients (Lai et al., 1998). Their findings support the notion that among other diseases in immune-complex-mediated glomerulonephritis the intrarenal activation of the RAS may be of pathogenic relevance.

The beneficial effect of blocking angiotensin II generation or its receptors appear to involve both hemodynamic (Navar et al., 1996; Kim and Iwao, 2000) and nonhemodynamic, cytokine-mediated mechanisms (Hisada et al., 1999; Nataraj et al., 1999).

Recent evidences points toward additional effects of RAS inhibition to influence immunological factors such as chemokines. For example, ACE inhibition results in a reduction of proteinuria and renal tissue damage through a reduction of CCL2/MCP-1 synthesis in immune complex nephritis in rats (Ruiz-Ortega et al., 1998). Both treatments with ACEI and AT1 receptor antagonists reduced CCL2/MCP-1 mRNA synthesis in unilaterally ureter-ligated rats (Morrissey and Klahr, 1998) and in a model of diabetic nephropathy in rats (Kato et al., 1999). In addition, AT1a-deficient mice were protected against antiglomerular basement membrane nephritis compared with wild-type control mice and showed less CCL2/MCP-1 and transforming growth factor-β production (Hisada et al., 1999). Finally, in vitro studies have shown the influences of angiotensin II on cellular immune responses

ABBREVIATIONS: RAS, renin-angiotensin-system; ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; MCP-1, monocyte chemotactic protein-1; BP, mean arterial blood pressure; ELISA, enzyme-linked immunosorbert assay; RPA, ribonuclease protection assay; IC, immune complex; CCL, CC chemokine ligand; CXCL, CXC chemokine ligand; RANTES, regulated on activation normal T cell expressed and secreted.
through a calcineurin-dependent pathway (Nataraj et al., 1999).

The aim of the present work was to study effects of angiotensin II blockade on the immune-complex-mediated renal damage in MRL/lpr mice. These mice develop a spontaneous autoimmune disease, which shows similarities to human systemic lupus erythematosus (Theofilopoulos and Dixon, 1981). The apoptosis-related fas gene in this mouse strain is modified carrying the mutation called lpr, which results in an aberrant transcript and a nonfunctional protein (Adachi et al., 1993). Autoreactive lymphocytes escape thymic selection (Merino et al., 1993), start their proliferation, and produce antibodies against own cell structures. As a consequence, circulating immune complexes are produced and deposited in the renal glomerular microvasculature. There, immune complexes trigger the synthesis of various mediators of inflammation, resulting in cellular infiltration, proteinuria, and progressive renal failure. In previous studies, we and others demonstrated that chemokine expression appears as an early molecular process contributing to the inflammatory process of lupus nephritis in mice (Zoja et al., 1994; Tesch et al., 1999; Pérez de Lema et al., 2001). Similar observations on the roles of chemokines have been reported for patients with lupus nephritis (Rovin et al., 1994; Wada et al., 1996). In addition, CCL2/MCP-1-deficient MRL/lpr mice show a reduction in nephritis (Zoja et al., 1997; Tesch et al., 1999; Pérez de Lema et al., 2001). Similar observations on the roles of chemokines have been reported for patients with lupus nephritis (Rovin et al., 1994; Wada et al., 1996). In addition, CCL2/MCP-1-deficient MRL/lpr mice show a reduction in renal mononuclear cell infiltrates and proteinuria leading to prolonged survival compared with wild-type or heterozygous lupus mice (Tesch et al., 1999). In the present study, we therefore tested the hypothesis that inhibition of the angiotensin II system would ameliorate renal inflammation in MRL/lpr mice by reducing the expression of chemokines. By contrast, comparable reduction in mean arterial blood pressure (BP) by the calcium antagonistamlodipine might not have such a protective effect, a hypothesis supported by our results.

Materials and Methods

Reagents and Antibodies. The following antibodies were used: a rabbit anti-mouse Ki-67 antiserum (Dianova, Hamburg, Germany), a fluorescein isothiocyanate-conjugated rabbit anti-mouse IgG antibody (Boehringer Mannheim, Mannheim, Germany) and a peroxidase-conjugated goat anti-rabbit IgG secondary antibody (Dako, Glostrup, Denmark). All reagents for the anti-DNA enzyme-linked immunosorbent assay (ELISA) were from Boehringer Mannheim, except the mouse monoclonal anti-single- and double-stranded DNA antibody used as a standard (Chemicon International, Temecula, CA). Radiolabeled [α-32P]UTP (3,000 Ci/mmol) for RNase Protection Assay was from PerkinElmer Life Sciences (Boston, MA). All other reagents or solvents (analysis grade) were from Merck (Darmstadt, Germany). The multiprobe ribonuclease protection assay (RPA) template set mCK5 lacking the IP-10 probe was from BD PharMingen (San Diego, CA). Polyethylene glycol 6000 at 0.1% w/v, 0.1% ethanol (w/v), 2.0 mM NaHCO3 in aqua ad injectabilia (Braun, Melsungen, Germany) served for a vehicle for the administration of the drugs (Mackenzie et al., 1994). Candesartan cilexetil (candesartan) drug was obtained from Takeda Chemical Industries, Ltd. (Osaka, Japan). Xanef injectable solution (1 mg/ml) from MSD and Norvasec from Pfizer Central Research (Sandwich, Kent, UK) were the galenic forms used for the enalapril and amlopidine treatments, respectively.

Experimental Design. MRL/Mp-Tnfrs59Fas80 (MRL/lpr) mouse line was obtained from The Jackson Laboratory (Bar Harbor, ME) and bred and housed under specific pathogen-free conditions, with free access to water and food. All animal experimental procedures were performed in Germany after authorization by the local ethical committee according to German law (211-2531-83/2000). Female virgins MRL/lpr mice were randomly distributed into the different experimental groups and kept individually. Beginning at the age of 8 weeks, mice were treated (by adding the drug daily to 5 ml of drinking water) with 1) vehicle, 2) enalapril (3.0 mg/kg b.wt.), 3) candesartan (5.0 mg/kg), and 4) amlopidine (10.0 mg/kg). These dosages are within the usual therapeutic ranges used in mice (Tarkowski et al., 1990; Traynor and Schermann, 1999). The completeness of the treatment was assessed daily by measuring the amount of fluid consumed. Mice showing irregular intake and those who took less than 80% of the mean dose were rejected for further analysis. For each group, 9 to 12 mice were finally analyzed. Spot urine and blood samples were obtained every 2 weeks. The following parameters were determined using standard analytical protocols: albuminuria assessment by ELISA (Bethyl Laboratories, Montgomery, TX), Jaffe method (Bartels et al., 1972) for creatinine measurements (Merck Diagnostic), urease/glutamate dehydrogenase method (Hoffmann, 1971) for blood urea nitrogen measurements (Merck Diagnostika), ELISA for analysis of circulating IgG (Boehringer Mannheim), and anti-double-stranded DNA antibodies (Pietzko and Peters, 1981).

After BP measurement (see below), mice were sacrificed. One kidney was used exclusively for isolation of total RNA using a standard protocol (Chomczynski and Sacchi, 1987). The other kidney was split into two halves. One half was fixed in formaldehyde for routine histological examination or immunohistological studies. The other half of the renal tissue was embedded in tissue-freezing medium (Jung; Leica Instruments, Wetzlar, Germany), snap-frozen in liquid nitrogen, and stored at −80°C until used for immunohistological studies.

Measurement of Blood Pressure. At 14 weeks of age, BP was determined as previously described (Stauss et al., 1999). Mice were anesthetized by a single intraperitoneal injection of fentanyl, midazolam, and medetomidin (0.05, 5.0, and 0.5 mg/kg b.wt., respectively). The left femoral artery was exposed and cannulated by a polyethylene tube. The arterial catheter was connected to a pressure transducer located at the same level as the mice (Statham, Costa Mesa, CA) via a swivel device (Instech Laboratories, Inc., Plymouth Meeting PA). After surgery, naloxon, flumazenil, and atipamezole (1.2, 0.5, and 2.5 mg/kg b.wt., respectively) were injected s.c. to antagonize the effect of the anesthetic drug. Thus, the mice recovered from anesthesia within 5 to 10 min. In pilot experiments, we found that arterial pressure stabilized within 90 min and did not change significantly in the next 6 h. Therefore, pressure was determined continuously for 60 min, starting 90 min after injection of the antagonists. The pressure signal was processed with a computer-based monitoring system (XmAD; ftp://sunsite.unc.edu/pub/Linux/ science/lab) at a sampling rate of 1,000 Hz. Heart rate was calculated by analyzing software (XmANA) from the amplitude of the pressure signal.

Light Microscopy. Renal tissue was fixed in neutral buffered formaldehyde in saline, and 3- to 4-μm, paraffin-embedded sections were stained with H&E and periodic acid-Schiff stain. Glomerular injury was semiquantified by a renal pathologist blinded for the treatments considering glomerular hypercellularity, leukocyte exudation, and mesangial matrix expansion. Each of these parameters was graded as 0 (absence), 1+ (mild), 2+ (moderate), or 3+ (severe) and a glomerular index defined as the simple sum of all values. Interstitial cell infiltrates affecting the renal cortex and with a peritubular and pericapillar distribution were similarly graded as 0 to 3+.

Immunohistochemistry. Studies were performed on frozen tissue sections and processed as described above, using standard techniques (Mampaso and Wilson, 1983). Direct immunofluorescence studies were performed on 5-μm, ether/ethanol-fixed, cryostat sections by using fluorescein isothiocyanate-conjugated rabbit anti-mouse IgG antibody. Ki-67-positive cells were characterized on par-
affin-embedded tissue (5-µm thick sections) from four independent mice per group. Peroxidase-conjugated goat anti-rabbit IgG secondary antibody (DAKO) was always developed with diaminobenzidine as chromogen. Respective preimmune sera or matched isotype IgG control served as negative controls. The quantification of Ki-67 staining was performed by a pathologist blinded for the treatments by counting 50 glomeruli of four independent mice per group.

**Renal mRNA Expression.** Chemokine expression was analyzed by a commercial RPA, as previously described (Luckow et al., 2000). Twenty micrograms of total RNA from each sample was used. The RNase-protected probes were separated on 5% denaturing polyacrylamide gels and analyzed by PhosphorImaging (Storm 840 PhosphorImager; Molecular Dynamics, Sunnyvale, CA). Bands were quantified using ImageQuant software (Molecular Dynamics, Eugene, OR).

**Statistical Analyses.** Data were expressed as the means ± standard deviation and analyzed with either the unpaired two-way analysis of variance and t test with Bonferroni correction (for parametric data) or the Kruskal-Wallis and Mann-Whitney U test (for nonparametric data) as needed. The null hypothesis was rejected at p < 0.05.

**Results**

**Arterial Blood Pressure.** To rule out different effects of ACEI or AT1 antagonists versus calcium antagonists, BP was determined after 6 weeks of treatment by direct arterial measurement at 14 weeks of age. In MRL/lpr mice with progressive renal disease, treatment with amlodipine, enalapril, or candesartan (n = 5 in all groups) resulted in comparable and significant BP reduction compared with vehicle-treated controls (Fig. 1). No significant differences in the heart rate were observed between the groups (vehicle: 417 ± 40 beats/min; enalapril: 433 ± 18; candesartan: 413 ± 35; amlodipine: 474 ± 35) (n = 5).

**Plasma IgG and Anti-DNA Antibody Levels.** Total plasma IgG concentration increased with age in all groups. At 14 weeks of age, no significant differences between enalapril-, candesartan-, amlodipine-, or vehicle-treated MRL/lpr mice were observed (Fig. 2A). Similarly, plasma levels of anti-DNA antibodies (Fig. 2B) were comparable in all groups at 14 weeks of age.

**Renal Morphological Findings.** At the age of 8 weeks, when treatment had begun, no renal histological lesions were apparent (data not shown). At 14 weeks of age, untreated MRL/lpr mice showed well established renal alterations in both glomerular and tubulointerstitial compartments (n = 12). Glomerular lesions were characterized at this time point by enlarged, hypercellular glomeruli, with increased numbers of both resident cells and infiltrating leukocytes, as well as mesangial matrix expansion (Fig. 3A). Interstitial lesions included the presence of peritubular and pericapillary mononuclear cell infiltrates, which were focally and irregularly distributed through the whole cortex of the affected kidneys. As in human lupus, these lesions are very mild. By contrast to these mild interstitial lesions, the presence of large accumulations of lymphoid cells located in the medulla and around big renal vessels is a hallmark of nephritis in MRL/lpr mice.

As shown in Fig. 3, C and D, the development of glomerular lesions was reduced by 6 weeks of treatment with either enalapril (n = 12) or candesartan (n = 11), which reduced glomerular hypercellularity and mesangial matrix expansion compared with age matched, vehicle-treated MRL/lpr mice (Fig. 3A). Amlodipine treatment (n = 10) had no significant effect on glomerular lesions (Fig. 3B). Glomerular components of the renal disease were evaluated as described above. This glomerular injury score was significantly reduced by enalapril or candesartan compared with both vehicle and amlodipine control groups (Fig. 4B). In spite of the improvement of the glomerular lesions, none of the treatments had an effect on the lymphoproliferative interstitial findings (Fig. 3, E and F).

**Renal Immune Complex Deposition.** To examine whether differences in immune complex (IC) deposition might be a factor in the enalapril or candesartan-mediated effects, IC deposition was examined. At 14 weeks of age, mice of all groups showed similar IgG-immune complex deposition patterns in the kidneys (n = 3 in each group). IC deposits were generalized, diffuse, granular, and irregularly distributed within the mesangium. No significant differences were observed in either the localization or the intensity of the staining between the different treatment groups (Fig. 3, G–I). In some kidneys, positive nuclear staining corresponding to anti-nuclear antibodies was observed. None of the treatments had any effect on this staining pattern, however.

**Proteinuria and Blood Urea Nitrogen Levels.** Vehicle-treated MRL/lpr mice showed progressive increase in albuminuria from age 8 to 14 weeks. Amlodipine treatment caused a slight nonsignificant reduction of urinary albumin compared with vehicle-treated mice. Enalapril or candesartan treatment reduced albuminuria at week 14 compared with both vehicle and amlodipine-treated mice (Fig. 4A) (n = 10–12/group). Blood urea nitrogen as a coarse measure of renal function was comparable in all groups (enalapril: 17.5 ± 2.6; candesartan: 25.5 ± 4.09; vehicle: 21.3 ± 1.9 mg/dl; amlodipine: 23 ± 2.9 mg/dl).

**Mesangial Proliferation.** Mesangial expansion with increased cellularity and matrix was prominent in vehicle-treated, 14-week old MRL/lpr mice. Enalapril and candesartan treatment resulted in marked reduction of mesangial proliferation. As a marker of proliferating cells, we used the staining with Ki-67, which specifically recognizes proliferating cells (Scholzen and Gerdes, 2000). Renal sections from

![Fig. 1. Effect of treatments on arterial blood pressure in MRL/lpr mice.](image-url)
14-week old vehicle-treated mice showed prominent staining for the cell proliferation marker Ki-67. By contrast, both enalapril and candesartan treatments lead to a significant glomerular reduction of staining for Ki-67 (Fig. 4C). Kidneys from amlodipine-treated mice showed Ki-67 staining comparable with the vehicle-treated group.

**Chemokine Expression.** Our previous results had shown marked up-regulation of chemokine expression in kidneys from nephritic MRL/lpr mice (Pérez de Lema et al., 2001). To test the effect of the treatment, chemokine mRNA expression was analyzed by RPA of total kidney RNA. As shown in Fig. 5, enalapril or candesartan treatment reduced the renal expression of the chemokines CCL2/MCP-1, CCL4/MIP-1β, and CXCL1/MIP-2 by 50 to 70% compared with vehicle-treated controls. This reduction was statistically significant for the case of the reduction of CCL2/MCP-1 expression after both enalapril and candesartan treatments and for CCL4/MIP-1β in the candesartan group. The same trend was observed for the case of CXCL1/MIP-2 expression in both RAS blocking treatments and for CCL4/MIP-1β in enalapril-treated mice, but these differences did not reach statistical significance. By contrast, CCL5/RANTES expression was unaffected by RAS inhibition. As amlodipine had no effect on renal lesions and function, chemokines were not determined in this group.

**Discussion**

In the present work, we have studied the effects of the treatment with an ACE inhibitor (enalapril), an AT1 receptor antagonist (candesartan), or a calcium antagonist (amlodipine) on renal damage in a model of lupus-like disease in MRL/lpr mice. Based on previous experiments (Pérez de Lema et al., 2001), we chose the age of 8 weeks to start the treatment, as at that age no renal alterations are evident. A treatment period of 6 weeks was chosen, as at the age of 14 weeks well established renal lesions and increased proteinuria are observed (Pérez de Lema et al., 2001). Our results indicate that the treatment with either 3 mg/kg enalapril or 5 mg/kg candesartan, but not with 10 mg/kg amlodipine, had
a protective effect on renal, and specifically glomerular, damage. Both treatments having angiotensin II as a target resulted in a marked reduction of albuminuria as well as in glomerular renal damage compared with that observed in either amlodipine or vehicle-treated mice. At week 14 of age, amlodipine- or vehicle-treated mice showed proliferation and numerous Ki-67 positive cells in the glomeruli, which were markedly reduced in glomeruli of enalapril or candesartan-treated kidneys. The presence of peritubular and pericapillary mononuclear cell infiltrates was very mild and irregular at this age even in kidneys of vehicle-treated mice, arguing for a specific role of angiotensin II in the glomerular damage. The lymphoproliferative perivascular mononuclear cell infiltrates observed were not affected by angiotensin II-inhibition. This lesion is very characteristic of the MRL/lpr lupus model and consists mainly of lymphocytes (Carvalho-Pinto et al., 2002) and is most likely a sign of the lymphoproliferative phenotype as a consequence of the fas mutation rather than a consequence of any inflammatory response.

Our findings extend previous reports (Herlitz et al., 1988; Tarkowski et al., 1990) describing a protective effect of captopril (30 mg/kg) and no effect of enalapril (6.0 mg/kg) treatment on survival. According to these findings, both ACEI reduced glomerular damage in a similar way, but only captopril significantly prolonged the survival. Surprisingly, while captopril reduced blood pressure at 14 to 17 weeks compared with vehicle-treated controls, enalapril did not show this hypotensive effect at this age, whereas at later time points enalapril reduced blood pressure (Tarkowski et al., 1990). We observed a significant reduction of blood pressure at 14 weeks with enalapril. A possible explanation for this finding is that blood pressure was measured by tail plethysmography in Tarkowski’s study, whereas we used direct intraarterial determination.

The renoprotective effects of angiotensin II blockade have been attributed to both hemodynamic-dependent and -independent mechanisms (Navar et al., 1996; Hisada et al., 1999; Nataraj et al., 1999; Kim and Iwao, 2000). To exclude effects
of lowering the BP on the renal effects of the angiotensin II blockade, we included amlodipine-treatment in an additional group of mice. The observed protection of angiotensin II inhibition on glomerular damage in MRL/lpr mice could not be attributed exclusively to a reduction in BP by enalapril or candesartan, as amlodipine-treatment resulted in a comparable reduction in BP without a significant amelioration of albuminuria or histopathological glomerular damage. Obviously, this only excludes systemic BP as a factor, whereas intraglomerular hydrostatic pressure would be expected to be reduced by angiotensin II inhibition compared with the treatment with a calcium antagonist (Zanchi et al., 1995). As we did not measure the glomerular intracapillary hydrostatic pressure, a reduction in intraglomerular pressure by angiotensin II blockers remains a likely contributing factor for the beneficial effect observed. In fact, a decrease in intraglomerular hydrostatic pressure is considered a major renal therapeutic effect of angiotensin II blockers (Hollenberg, 2000).

Our experimental results strongly argue against differences in circulating IgG or anti-DNA antibodies or their glomerular deposition as reasons for the mitigation of disease in ACEI- or AT1 receptor antagonist-treated MRL/lpr mice. On the other hand, we cannot exclude that angiotensin II inhibition could affect the uptake of immune complexes. It is known that angiotensin II enhances phagocytosis of immune complexes by mesangial cells and macrophages (Singhal et al., 1990). If this also occurs in vivo, it remains unclear if this would be beneficial or detrimental for the immune complex nephritis. As immune complex deposition was unaltered, however, angiotensin II-dependent changes in their handling remains only a remote possibility.

The greatest effect of the angiotensin II inhibition was observed in the glomeruli and consequently resulted in a significant reduction of proteinuria. A significant reduction of mesangial expansion could be observed in enalapril- or candesartan-treated mice compared with vehicle- or amlodipine-treated mice. RAS-inhibition reduced mesangial cell proliferation as shown by immunostaining for Ki-67, a cell proliferation marker. This observation opens the possibility for an additional, nonhemodynamic pathophysiological mechanism: angiotensin II could increase the glomerular expression of mediators such as growth factors, chemokines, and cytokines. These mediators would modulate different processes, like the inflammatory cell recruitment or mesangial cell expansion.

Therefore, we further analyzed the expression of different chemokines. In a previous study, we described that several chemokines (preferentially CCL2/MCP-1 and CCL5/RANTES) are up-regulated early in glomeruli of MRL/lpr mice (Pérez de Lema et al., 2001). Chemokines contribute to the progression of the disease by promoting the recruitment of leukocytes into the kidney. At the 14-week time point analyzed, the major locations of CCL2/MCP-1 and CCL5/RANTES expression are the glomeruli (Pérez de Lema et al., 2001), which also corresponded to the sites of cellular infiltration and proliferation. According to our results, the blockade of angiotensin II differentially reduces the expression of some chemokine mRNA, such as CCL2/MCP-1, CXCL1/MIP-2, and CCL4/MIP-1β. It has been described that AT1 receptor antagonist treatment reduces CCL2/MCP-1 expression and monocyte/macrophage infiltration in an antithymocyte serum-induced glomerulonephritis (Wolf et al., 1998).

ACE inhibition also decreased recruitment of mononuclear cells in a rat model of immune complex nephritis through down-regulation of CCL2/MCP-1 and nuclear factor-κB inactivation (Ruiz-Ortega et al., 1998). Furthermore, treatments with ACEI or AT1 receptor antagonists reduced CCL2/ MCP-1 mRNA synthesis in kidneys from rats with unilateral ureter ligation (Morrissey and Klahr, 1998).

Surprisingly, in our lupus-nephritis model, CCL5/RANTES mRNA remained unaltered in enalapril or candesartan treatment groups compared with vehicle-treated mice. Wolf et al. (1997) found that angiotensin II can stimulate the expression of CCL5/RANTES both in vitro and in vivo. Incubation of cultured rat glomerular endothelial cells or infusion of angiotensin II into rats resulted in an increase of CCL5/ RANTES expression, an effect that was surprisingly mediated by AT2-receptors and independent of AT1 (Wolf et al., 1997). The unaltered mRNA levels for CCL5/RANTES in the present study remain unexplained at present.

Undisclosed is the question whether chemokine expression is directly reduced by the RAS blockade or whether the lower chemokine expression is an indirect effect of reduced inflammation. Effects of angiotensin II blockade on chemokine generation have been previously reported (Ruiz-Ortega et al., 1998; Wolf et al., 1998), but an intermediate role of other mediators of inflammation was not considered, although probably a network of different cytokines acting synergistically are involved.

Our results indicate that angiotensin II inhibition has protective effects on the development of immune-mediated renal damage, an effect that involves not only hemodynamic but also immune-modulatory effects. We suggest that the antihypertensive effect of AT1 blockers or ACEIs is an important but not exclusive mechanism by which the progression of renal disease is achieved. Through a reduction of chemokine expression, the inhibition of the RAS would modulate the immune response in lupus nephritis and other nephropathies and thereby ameliorate the renal damage.

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References


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