Upregulated Expression of Rat Heart Intercellular Adhesion Molecule-1 in Angiotensin II– but Not Phenylephrine-Induced Hypertension

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Abstract—Intercellular adhesion molecule-1 (ICAM-1), part of an immunoglobulin-like superfamily of adhesion molecules, is involved in several cardiovascular diseases. We investigated whether in vivo angiotensin II (Ang II) increases ICAM-1 in rats. Sprague-Dawley rats were infused with vehicle or Ang II (750 μg · kg⁻¹ · d⁻¹ SC) for 7 days. The contribution of Ang II receptors to ICAM-1 expression was investigated with a nonpeptide Ang II type 1 (AT₁) receptor antagonist losartan (30 mg · kg⁻¹ · d⁻¹ in drinking water). Systolic blood pressure was elevated in Ang II–treated animals compared with sham-treated controls, and losartan blocked this increase. Tumor necrosis factor (TNF)-α (5 μg/kg IP bolus), a prototype inducer of ICAM-1, was administered as a positive control for ICAM-1 expression. After treatment, hearts were frozen in liquid nitrogen; homogenates were subjected to SDS-PAGE and immunoblotted with an anti-rat ICAM-1 monoclonal antibody. We detected a predominantly high-molecular-weight band in homogenates from non–TNF-α–treated rats, which was enhanced by 80±5% in TNF-α–treated rats. This band measured ≈200 kDa, which is the molecular weight of ICAM-1 in its native dimer form. The same band was detected in homogenates from sham and Ang II–treated rats, with the latter showing a 150±10% increase in ICAM-1 versus sham controls. Immunoprecipitation of rat heart homogenates with anti-rat ICAM-1 antibody resulted in a dominant band of the same molecular weight as samples not treated with antibody. Losartan prevented enhanced expression of ICAM-1 in the presence of Ang II but had no effect on basal ICAM-1 expression. Phenylephrine, an α-agonist (3 mg · kg⁻¹ · d⁻¹ ), was infused for 1 week but had no effect on ICAM-1 expression, even though systolic blood pressure was elevated to the same level as in rats treated with Ang II. Thus, heart ICAM-1 expression is enhanced via AT₁ receptor activation independent of hypertension. Ang II–induced ICAM-1 expression was time and dose dependent, with maximal expression occurring within 5 to 7 days at 100 to 750 μg/kg Ang II. Immunohistochemical staining demonstrated markedly increased ICAM-1 levels in the perivascular area in Ang II–infused rats. Monocyte/macrophage accumulation was significantly greater in Ang II–treated rat hearts than in sham-treated hearts (10±1; P<0.001; n=5). Thus during inflammation, overexpression of ICAM-1 may contribute to cardiovascular damage in diseases characterized by increased activity of the renin-angiotensin system. (Hypertension. 2001;37:58-65.)

Key Words: angiotensin II □ cell adhesion molecules □ hypertension, experimental □ losartan □ phenylephrine

Intercellular adhesion molecule-1 (ICAM-1) is a member of an immunoglobulin-like superfamily of adhesion molecules that are involved in physiological and pathophysiological functions such as cell–cell interaction, inflammation, and sepsis,1 as well as several cardiovascular diseases, including ischemia-reperfusion, shock-resuscitation, atherosclerosis and thrombosis, hypercholesterolemia, and myocardial infarction.1–3 ICAM-1 is a glycoprotein with a molecular weight of ≈200 kDa4 that is expressed on a variety of cell membranes, including endothelial cells, leukocytes, and fibroblasts.5 Interaction of ICAM-1 with leukocyte receptors mediates firm adhesion and emigration of leukocytes, which plays a major role in their passage (‘trafficking’) through normal and inflamed tissues.6,7 Accumulation of monocytes and lymphocytes in the vessel wall is a hallmark of the early stages of diseases, such as atherosclerosis, as well as of vascular injury.8,9 Several studies have implicated ICAM-1 as a key component in the pathogenesis of a variety of acute and chronic inflammatory diseases. Recent reports have shown blunted infiltration of leukocytes in ischemia-reperfusion in animals receiving monoclonal antibodies against ICAM-1.9 When myocardial ischemia-reperfusion injury was induced in mice genetically deficient in ICAM-1, similar reductions in polymorphonuclear leukocyte infiltration were observed.10

Studies suggest a correlation between augmented angiotensin II (Ang II) and the development of cardiac ischemia.11,12 Although ACE inhibitors have been shown to have several cardiovascular protective effects,11,13–16 the mechanisms of

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action are not fully understood. In congestive heart failure, ACE inhibitors have been shown to reduce left ventricular hypertrophy and to improve cardiac function,\(^{17}\) while in atherosclerosis, ACE inhibitors can reduce the development of lesions, restore impaired endothelial function, and decrease neointimal hyperplasia.\(^{14,16,18}\) It has also been shown that under pathophysiological conditions such as chronic heart failure and hypertension, Ang II plays an important role in the control of tissue structure.\(^{19,20}\)

In view of the possible relationship between Ang II and ICAM-1 expression in the pathophysiology of hypertension and vascular injury, the present study was designed to investigate whether in vivo expression of ICAM-1 is induced by Ang II. In addition, we examined the effect of elevated blood pressure per se on ICAM-1 expression and the cellular localization of ICAM-1 and monocyte/macrophage infiltration in response to Ang II in rat hearts.

**Methods**

**Animal Experiments**

Ten-week-old male Sprague-Dawley rats (average weight 300±25 g) were obtained from Charles River Laboratories. All animals were housed in individual cages and fed standard rat chow and tap water. On arrival, rats were allowed to adjust to their new environment for 7 to 10 days. Under ethyl ether anesthesia, osmotic minipumps (Alza 2 ML2) were implanted for drug infusion. This study was approved by the Henry Ford Hospital Care of Experimental Animals Committee.

**Experimental Protocols**

**Ang II Infusion With and Without Losartan**

The rats were divided into 4 groups. Two groups were infused with Ang II (750 μg·kg\(^{-1}\)·d\(^{-1}\) SC; Bachem)\(^{21,22}\) dissolved in saline with 0.01N glacial acetic acid (Sigma) at a rate of 5 μL/h for 1 week (days 8 to 14) and were given tap water with or without losartan (30 μg·kg\(^{-1}\)·d\(^{-1}\), Merck) for 2 weeks (days 1 to 14). The other 2 groups were infused with vehicle (sham, saline with 0.01N glacial acetic acid) for 1 week (days 8 to 14) and received tap water with or without losartan (30 μg·kg\(^{-1}\)·d\(^{-1}\) ) as described above.

**Ang II Dose and Time Dependence of ICAM-1 Induction**

Other groups of rats were infused with various doses of Ang II (10 to 750 μg·kg\(^{-1}\)·d\(^{-1}\)) or vehicle for 1 week as described above. Blood pressure was measured every 2 days. To examine time dependence, a subpressor dose of Ang II (100 μg·kg\(^{-1}\)·d\(^{-1}\)) was administered. Each Ang II–treated group had a control group that received vehicle. ICAM-1 expression was analyzed and quantified by Western blotting as described above.

**TNF-α Studies**

For comparison, TNF-α was used as a prototype inducer of ICAM-1. The effect of TNF-α (Endogen) on ICAM-1 expression was determined 5 hours after injection of a single dose (5 μg/kg IP bolus).\(^{23,24}\) The control group (sham) received PBS as vehicle (pH 7.4). Hearts were harvested 5 hours after TNF-α or PBS.

**Effect of Hypertension on ICAM-1 Expression**

To determine whether the effect of Ang II infusion is dependent on hypertension, we compared the effect of elevated blood pressure on ICAM-1 expression in rats treated with Ang II (750 μg·kg\(^{-1}\)·d\(^{-1}\)), phenylephrine (PE) (3 mg·kg\(^{-1}\)·d\(^{-1}\)), or vehicle (saline with 0.01N glacial acetic acid) for 1 week. All drugs were infused via osmotic minipump (Alza 2 ML2).

**Losartan Preparation**

To test the contribution of Ang II type 1 (AT\(_1\)) receptors to the effect of Ang II, we administered losartan before and during the infusion of Ang II or vehicle. Losartan was dissolved in tap water, and the concentration was adjusted for daily water intake and body weight to obtain an average dosage of 30 μg·kg\(^{-1}\)·d\(^{-1}\) for 2 weeks (days 1 to 14). This study was approved by the Institutional Animal Care and Use Committee.

**Systolic Blood Pressure Measurement**

Systolic blood pressure (SBP) was measured on day 0 (basal) and then every 2 or 3 days depending on the experiment (see figure legends) using the standard tail-cuff method (ITC/Life Science Instruments).

**Preparation of Tissue Samples**

At the end of the treatment period, all animals were anesthetized with thiobutabarbital (125 mg/kg IP Inactin; Promonta) and administered heparin (400 U/rat IP); they were then perfused with cold PBS (pH 7.4) via the left ventricle for 10 minutes. The heart was removed, washed with cold PBS, and immediately snap-frozen with liquid nitrogen and then stored at −80°C until use. For Western blots of ICAM-1, heart tissue was homogenized using a micro–tissue grinder (VWR) with ice-cold homogenization buffer (10 mmol/L Tris-HCl, pH 7.4, 100 mmol/L NaCl, 300 mmol/L sucrose, 1 mmol/L EDTA, 0.2 mmol/L PMSF, 2 mmol/L leupeptin, 2 mmol/L apstatin, 2 mmol/L amastatin). All protease inhibitors were obtained from Sigma. Homogenates were centrifuged at 13 000g and 4°C for 5 minutes, and the supernatant was collected. Protein concentration was determined with Coomassie Plus Protein Assay Reagent (Pierce).
Western Blot

An aliquot of homogenate containing 100 μg protein was diluted in the same volume of sample buffer (21.25% SDS nonreducing buffer, 10% glycerol, 2.5% bromophenol blue, 13.75% 0.5 mol/L Tris-HCl, pH 6.8), vortexed, and heated at 65°C for 5 minutes. Then, 1 to 3 μg of each sample was loaded into the wells, and proteins were separated out by SDS-PAGE on a 7.5% polyacrylamide precast gel (Owl) with a Mini-Protean II dual slab cell (Bio-Rad) at 4°C. Proteins were electroblotted to Hybond-P membranes (Amersham) in the presence of glycine/methanol buffer (pH 8.3).

Membranes were blocked with 5% nonfat dry milk in Tris-buffered saline (TBS; Bio-Rad) with 0.1% Tween-20 at room temperature for 1 hour, followed by 3 washes with TBS for 15 minutes each. They were then incubated with a 1:2000 dilution of anti-rat ICAM-1 monoclonal antibody raised in mice (1A29; Endo-gen) in TBS for 1 hour at room temperature, followed by 3 washes as above. Membranes were incubated with a 1:5000 dilution of peroxidase-conjugated goat anti-mouse IgG (Sigma) in 0.5% nonfat dry milk (TBS) at room temperature for 1 hour. After 3 washes, an ECL-Plus Chemiluminescence Detection System (Amersham) was used to visualize the bands. Autoradiograms were analyzed with an automatic densitometer (model GS-670; Bio-Rad).

Immunoprecipitation of Tissue Samples

Rat heart tissue homogenate (200 μL [1 g/L]) was either left untreated or was incubated with anti-rat ICAM-1 antibody (1:1000) at 4°C for 4 hours. Then, 20 μL of protein A–Sepharose beads (Sigma) was added to the homogenate and incubated with gentle rocking at 4°C for 1 hour. Protein was centrifuged at 4°C for 30 seconds, and the pellet was washed 3 times with lysis buffer (Sigma) and suspended with 20 μL lysis buffer. Associated proteins were characterized by Western blotting as described earlier.

Immunohistochemistry

Next, 4- to 5-μm sections of snap-frozen tissue were cut and dried for 1 hour at room temperature. Sections were fixed by acetic acid (Sigma) for 10 minutes and dried at room temperature. They were washed with PBS and blocked with goat serum (Sigma) (1:1000) for 30 minutes. Depending on the experiment, anti-rat ICAM-1 (Endo-gen) and/or anti-rat monocyte/macrophage monoclonal antibody (Chemicon) (1:1000) was added to tissue sections at 4°C and kept in a humidified chamber overnight. The primary antibodies were discarded, and sections were washed with PBS. ICAM-1 and monocyte/macrophage positive staining was detected with fluorescein-conjugated IgG secondary antibody (Amersham or Chemicon) treated at room temperature for 1 hour. Sections (5 fields per animal) were evaluated by a pathologist without knowledge of the treatment regimens. For each animal, sections were also stained with Gill No. 2 hematoxylin (Sigma) and eosin for 5 minutes and 1 minute, respectively.

Statistical Analysis

All values are expressed as mean±SEM of n observations, where n is the number of in vivo experiments. The results were analyzed by Student’s t test. *P<0.05 was considered significant.
Results

Between days 0 and 6, the SBP of all groups was in the basal range and did not differ between groups (Figure 1A). In rats treated with Ang II alone, SBP was significantly increased ($P < 0.05$; Figure 1A). Both groups treated with losartan remained in the basal range.

A predominantly high-molecular-weight band of $\approx 200$ kDa was observed on Western blots of heart homogenates using ICAM-1 monoclonal antibody as a probe (Figure 2A). A band of the same molecular weight was induced by TNF-$\alpha$. Rats treated with TNF-$\alpha$ showed a significant increase in heart ICAM-1 expression compared with sham-treated animals ($80 \pm 5\%$; $P < 0.05$; n=6; Figures 2A and 2B). Density was greatest in homogenates from Ang II–treated rats (Figure 2A).

ICAM-1 expression was visibly diminished in rats treated with both losartan and Ang II compared with those treated with Ang II alone (Figure 2A), and there was no difference in density between sham and losartan groups. In cumulative experiments, homogenates from Ang II–treated rats showed a marked increase in ICAM-1 expression compared with sham ($P < 0.05$; n=6; Figure 2B). Moreover, ICAM-1 protein was significantly blocked in rats treated with both losartan and Ang II ($P < 0.05$; n=6). Cumulative data also showed that losartan alone had no effect on average density.

To determine whether hypertension might be involved in the induction of ICAM-1, we examined the effect of PE on ICAM-1 expression. Both PE and Ang II caused a significant and sustained elevation in SBP compared with sham treatment ($P < 0.05$; n=5; Figure 1B). There was no significant difference in SBP between PE- and Ang II–treated rats on days 2, 4, and 6. Contrary to the effect of Ang II, Western blots showed that ICAM-1 was not induced in rats treated with PE (Figure 3A). In 5 experiments, PE did not induce ICAM-1 expression compared with sham treatment, whereas it was significantly induced with Ang II ($P < 0.05$; Figure 3B).

Upregulation of ICAM-1 expression by Ang II appeared to be dose dependent and became significant at 100 to 750 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$ (Figure 4A). However, only rats treated with the highest dose of Ang II (750 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$) became hypertensive (Figure 1B). To further examine the blood pressure–independent effects of Ang II, 100 $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ d$^{-1}$ Ang II was selected for the time course experiments. This dosage of Ang II increased ICAM-1 within 3 days, and maximal expression was observed within 5 to 7 days (Figure 4B).

Immunostaining for ICAM-1 was performed to investigate the localization of ICAM-1 within the heart. Intense immunolocalization of ICAM-1 was observed, mainly in the...
perivascular structures of the Ang II–treated rat heart (Figure 5C). Faint ICAM-1 immunostaining was observed in the sham-operated group (Figure 5B), while monocyte/macrophage accumulation in the heart was barely detectable (Figure 5D). On the other hand, hearts from Ang II–treated rats showed a 10±1-fold increase in monocyte/macrophage accumulation (Figure 5E; \( P<0.0001; n=5 \)) compared with sham-treated hearts. The pattern of accumulation was in accord with the increased ICAM-1 expression.

**Discussion**

The major finding of the present study was that Ang II resulted in upregulation of ICAM-1 expression in hearts from male Sprague-Dawley rats. No such increase was observed in Ang II–treated rats chronically administered the AT1 antagonist losartan or with hypertension induced by PE. Previous studies have quantified the expression of ICAM-1 through immunohistochemical approaches, radioimmunoassays, and binding studies in response to a variety of agonists. Our observations confirm the findings of Reilly et al.\(^4\) that ICAM-1 is expressed predominantly as a dimer with a molecular weight of \( \approx 200 \) kDa. They also showed that the dimer form of ICAM-1 has a higher affinity for binding to the lymphocyte function-associated antigen-1 receptor than the monomer, which represents a critical step in the inflammatory process.\(^4\) Because TNF-\( \alpha \) is well established as an inducer of ICAM-1,\(^23,24\) our demonstration that TNF-\( \alpha \) at a submaximal dose induces the same band as Ang II strongly supports the contention that the band induced by Ang II is ICAM-1. In early experiments, other bands with a molecular weight of \(<200 \) kDa were visible, and immune-precipitation of heart homogenates with anti-rat ICAM-1 antibody isolated the same \( \approx 200\)-kDa band. In subsequent experiments, we eliminated the need for immune precipitation by optimizing Western blot conditions (reducing nonspecific binding), and these conditions were used throughout the study. Unlike previous studies, our results suggest that immunoblotting can be used to quantify changes in ICAM-1 expression.

We found that Ang II–induced ICAM-1 upregulation was blocked in rats treated with both losartan and Ang II, whose SBP remained close to baseline throughout the treatment period. These data support direct mediation of ICAM-1 induction by the AT\(_1\) receptor. Indeed, AT\(_1\) receptor antagonists have been shown to reduce ICAM-1 in the renal cortex in high human renin transgenic\(^28\) and hydronephrotic rats.\(^29\) In human coronary endothelial cells, Ang II has been shown to induce E-selectin but not ICAM-1 or vascular cell adhesion molecule-1 (VCAM-1), and this induction was blocked by an AT\(_1\) receptor antagonist.\(^30\) On the contrary, there is evidence in the literature that ICAM-1 is induced in the coronary vessel endothelium during heart failure\(^31\) and in the renal blood vessel endothelium in rats transgenic for human angiotensinogen and renin genes.\(^28\) The fact that Ang II induced ICAM-1 production in whole hearts may represent a more complicated paracrine induction of ICAM-1 through the effects of Ang II on neighboring cells, including smooth muscle cells. The AT\(_1\) receptor antagonist losartan has been shown to reduce monocyte binding to the thoracic aorta in rats that exhibit long-term activation of the renin-angiotensin system, implying AT\(_1\) receptor–mediated induction of adhesion molecules for monocytes, including VCAM-1, P-selectin, and ICAM-1. However, we believe this is the first report of Ang II induction of ICAM-1 expression and blockade by an AT\(_1\) receptor antagonist in the heart. Because losartan completely lowered blood pressure in these rats, we could not exclude hypertension as a contributing factor in the regulation of ICAM-1 expression.\(^33–36\) We therefore carried out experiments designed to examine the effect of elevating blood pressure by other means on ICAM-1 levels. Rats were infused with PE, an \( \alpha \)-agonist, at a dosage chosen to produce the same level of SBP as in Ang II–treated rats.\(^21,22\) In contrast to Ang II, PE infusion (which produced similar data suggest that Ang II enhances ICAM-1 expression in a dose- and time-dependent manner via AT\(_1\) receptors and independent of the rise in blood pressure.

There have been conflicting reports regarding the molecular weight of ICAM-1 and whether it is present as a dimer or monomer.\(^4,26,27\) Our observations confirm the findings of Reilly et al.\(^4\) that ICAM-1 is expressed predominantly as a dimer with a molecular weight of \( \approx 200 \) kDa. They also showed that the dimer form of ICAM-1 has a higher affinity for binding to the lymphocyte function-associated antigen-1 receptor than the monomer, which represents a critical step in the inflammatory process.\(^4\) Because TNF-\( \alpha \) is well established as an inducer of ICAM-1,\(^23,24\) our demonstration that TNF-\( \alpha \) at a submaximal dose induces the same band as Ang II strongly supports the contention that the band induced by Ang II is ICAM-1. In early experiments, other bands with a molecular weight of \(<200 \) kDa were visible, and immune-precipitation of heart homogenates with anti-rat ICAM-1 antibody isolated the same \( \approx 200\)-kDa band. In subsequent experiments, we eliminated the need for immune precipitation by optimizing Western blot conditions (reducing nonspecific binding), and these conditions were used throughout the study. Unlike previous studies, our results suggest that immunoblotting can be used to quantify changes in ICAM-1 expression.

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hypertension) had no effect on ICAM-1 expression, strongly suggesting that Ang II–increased ICAM-1 expression is independent of hypertension and that Ang II activates ICAM-1 expression at the cellular level via the AT_1 receptor. Interestingly, a subpressor dosage of Ang II (100 μg · kg\(^{-1}\) · d\(^{-1}\)) significantly induced ICAM-1 expression without causing hypertension. This further suggests that Ang II is capable of upregulating ICAM-1 independent of increases in blood pressure. Because the time course data showed an increase in ICAM-1 expression on day 3 and maximal induction within days 5 to 7, it seems that unlike TNF-α, the effect of Ang II on ICAM-1 expression is not acute.

Our immunostaining data clearly showed that Ang II upregulates ICAM-1 expression predominantly in the coronary vasculature, as supported by previous reports,\(^2,10\) as well as the marked increase in monocyte/macrophage accumulation, which confirms the pathophysiological significance of upregulation of ICAM-1 by Ang II. Although monocyte/macrophage accumulation was examined primarily in rats treated with a high dosage of Ang II (750 μg · kg\(^{-1}\) · d\(^{-1}\)), our preliminary data showed that a subpressor dosage of Ang II (100 μg · kg\(^{-1}\) · d\(^{-1}\)) can also enhance monocyte/macrophage accumulation. This suggests that even subpressor concentrations of Ang II have pathophysiological significance. In addition, our data showed a significant reduction in monocyte/macrophage infiltration and accumulation in the thoracic aorta of mice treated with a high dose of Ang II (750 μg · kg\(^{-1}\) · d\(^{-1}\)) and coadministration of anti-ICAM-1 antibody (n=2).

These findings could have important and broad implications for damage related to heart failure and myocardial infarction\(^{17,19,37}\) when the renin-angiotensin system is activated. When circulating Ang II is elevated in these diseases, vascular damage may ensue due to Ang II–induced overexpression of ICAM-1 as a result of enhanced leukocyte binding.\(^{11,19,28}\) This increased binding could alter vascular function\(^2,10\) and either directly or indirectly promote damage to the heart. Direct injury to the heart may occur through the infiltration of monocytes into cardiac muscle. Indeed, a recent study showed that monocyte binding to ICAM-1 leads to reduced contractility of cardiac myocytes and suggested that this damage is mediated by reactive oxygen species.\(^{38}\) Indirect injury may be related to vascular endothelial dysfunction, which reportedly arises from monocyte binding to the endothelium\(^{39}\) associated with an increase in superoxide anion.\(^{40}\) Thus, chronic damage to the endothelium could lead to decreased nitric oxide bioavailability and, hence, increased peripheral vascular resistance, hypertension, and left ventricular hypertrophy. Alternatively, endothelial dysfunction may lead to reduced perfusion of the cardiac muscle and/or thrombosis, which in turn causes myocardial infarction. In rats with heart failure, ACE inhibitors and Ang II receptor antagonists had a cardioprotective effect,\(^{15}\) seen as increased

![Figure 5. Immunohistochemical analysis of ICAM-1 and monocyte/macrophage binding. Intense immunostaining of ICAM-1 was seen in the perivascular region (arrows) of the Ang II–treated rat heart (C), with a corresponding marked accumulation of monocyte/macrophage (arrows) (E). Faint ICAM-1 immunostaining was seen in the sham group (B), with hardly any monocyte/macrophage accumulation (D). There was a significant difference in monocyte/macrophage accumulation between Ang II–treated rats and sham (F). *P<0.001, n=5. A, H&E staining for rat heart.](http://hyper.ahajournals.org/Downloadedfrom)
left ventricular function and decreased collagen deposition. Over the long term, Ang II–induced ICAM-1 may contribute to the development of atherosclerosis through the recruitment of blood-borne monocytes and formation of foam cells by macrophages. This contention is supported by the demonstration that ACE inhibitors reduce the formation of foam cells and development of atherosclerotic lesions in the rabbit thoracic aorta. Ang II is known to cause proliferation of smooth muscle cells with disruption of the endothelium, and changes in vascular permeability may play an important initiating role in the pathogenesis of atherosclerosis. Upregulation of ICAM-1 by Ang II may exacerbate this progression by increasing the recruitment of leukocytes, followed by adhesion and transmigration, resulting in further endothelial cell damage and microvascular dysfunction.

Hence, early increased expression of ICAM-1 caused by Ang II may be an important initiating event in target organ damage in diseases characterized by activation of the renin-angiotensin system. Furthermore, our data suggest that rises in Ang II independent of elevations in blood pressure may initiate damage. On the other hand, hypertension not associated with increased Ang II may be less likely to cause cardiovascular damage.

In summary, Ang II appears to stimulate ICAM-1 expression directly via the AT(1) receptor in adult rat hearts. Rats treated with the AT(1) receptor antagonist losartan showed normal ICAM-1 expression. Overexpression of ICAM-1, which is involved in inflammation, may contribute to cardiovascular damage in diseases characterized by increased activity of the renin-angiotensin system with or without hypertension. Together, these data support the use of losartan as a pharmacological intervention, not only to ameliorate hypertension but also to prevent end-organ damage.

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References


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