Original Article

Effects of the Angiotensin II Type 1 Receptor Antagonist Telmisartan on Monocyte Adhesion and Activation in Patients with Essential Hypertension

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Circulating monocytes from hypertensive patients show elevated secretion patterns of pro-inflammatory cytokines, an increased expression of adhesion molecules, and an increased adhesion to vascular endothelial cells. We tested the hypothesis that telmisartan, an angiotensin II type 1 (AT_1) receptor antagonist, reduces the activation of circulating monocytes from hypertensive patients and diminishes the monocyte–endothelial cell adhesion. Monocytes of 20 hypertensive patients and 20 normotensive controls were isolated by density gradient centrifugation and Dynabeads, and the monocyte adhesion to human aortic endothelial cell monolayers was measured by adhesion assays. To characterize monocyte activation we assessed the expression of activity-related cell surface markers that are also involved in monocyte adhesion to endothelial cells, such as CD11a/b and CD54, as well as the chemokine receptors CCR1, CCR2 and CCR5 before and after telmisartan therapy using flow cytometry. Spontaneous adhesion of monocytes from hypertensive patients and the adhesion after stimulation with angiotensin II were significantly increased compared with those in normotensive controls ($p<0.05$). Treatment of hypertensive patients with the AT_1 receptor antagonist telmisartan significantly diminished the adhesion of circulating monocytes to human endothelial cells ($p=0.02$) despite the increase in the expressions of CD11b, CD54 and CCR5 after telmisartan therapy. Reducing monocyte adhesion may be a novel beneficial effect of the AT_1 receptor antagonist telmisartan helping to prevent vascular alterations in hypertension. The mechanism of action remains to be elucidated, since reduction in monocyte adhesion was not attributable to changes in adhesion molecule expression. (*Hypertens Res* 2007; 30: 521–528)

***Key Words*: telmisartan, monocyte, adhesion, chemokine, hypertension**

Introduction

Hypertension is a major risk factor for the development of atherosclerotic vascular disease (*1*). However, the specific pathways leading from hypertension to atherosclerosis are not completely understood (*2*, *3*).

Since the nineties it has been accepted that atherosclerotic lesions are associated with signs of inflammation and that the adherence and transendothelial migration of circulating monocytes into the intima is an important step in the systemic inflammatory response resulting in the development of atherosclerosis (*4*).

The adhesion process of leukocytes is a multi-step cascade involving interaction of endothelial selectins with their respective ligands, which results in rolling of leukocytes. This

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allows the subsequent interaction between chemokines presented by the endothelial cells with their G-protein coupled receptors on leukocytes. Ligation of chemokine receptors activates integrins, which facilitate firm adhesion by interaction with so-called intercellular adhesion molecules (ICAMs) (*5*, *6*).

The transendothelial migration of monocytes from the vessel to the interstitium represents a normal physiological process (*7*) that plays a crucial role in the restitution of tissue-resident macrophages. Under conditions of certain diseases or infections, the recruitment of leukocytes into peripheral tissues can be enormously amplified due to the action of cytokines, which induce the expression of adhesion molecules on endothelial cells as well as on monocytes, promoting the adhesion of both (*8*).

This process is important not only for the initiation of acute and chronic inflammation but also for the progression to advanced phases of chronic vessel diseases (*9*). For instance, McCarron *et al*. (*10*) showed a significant increase of monocyte adhesion to endothelial cells from spontaneous hypertensive rats (SHR) *vs*. that to endothelial cells from normotensive Wistar-Kyoto rats after stimulation with lipopolysaccharide (LPS) or pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α). In contrast, inhibition of cell adhesion can induce anti-inflammatory effects and stabilize atherosclerotic plaques (*11*).

Increased secretion of pro-inflammatory cytokines by circulating monocytes has been reported in patients with essential hypertension, suggesting that these cells are pre-activated in hypertensive patients (*12*), and single nucleotide polymorphisms in the interleukin-6 gene have been associated with blood pressure and atherosclerosis (*13*).

Furthermore, monocytes of hypertensive patients showed a significantly higher adherence to human endothelial cells compared to those of normotensive controls (*14*). The monocyte activation of patients with essential hypertension was also confirmed by an increased production of superoxide by these cells. This fact helps to explain the premature atherosclerosis of hypertensive patients.

Since the eighties it has been well known that hypertensive patients show an activation of the renin-angiotensin system, and that one-third of them have increased levels of angiotensin II (Ang II). In addition to its effects on blood pressure, Ang II has been shown to be involved in the inflammatory vascular process, as it activates circulating cells, including monocytes, and mediates endothelial dysfunction (*12*, *15*, *16*). For instance, Ang II stimulation enhances the production of pro-inflammatory cytokines from monocytes and the expression of adhesion molecules on monocytes (*12*). The blocking of Ang II activity by angiotensin converting enzyme inhibitors or Ang II type 1 (AT_1) receptor antagonists has been shown to result in anti-inflammatory effects and prevent or reduce the development of atherosclerosis in animal models. In humans, the anti-inflammatory effects of these agents have been suggested by a study of Vazquez-Oliva *et al*., which showed that treatment with the AT_1 receptor antagonist irbesartan decreased blood pressure in hypertensive patients in parallel with an decrease in serum interleukin (IL)-6 to levels similar to those in normotensive individuals (*17*). Sanada *et al*. reported that the elevation of serum soluble E- and P-selectin in patients with hypertension is preserved by benidipine, a long-acting calcium channel blocker (*18*).

There is still a dearth of large controlled studies with AT_1 receptor antagonists, despite the known anti-inflammatory properties of these agents (*19*–*21*). Uchida *et al*. verified the practical efficacy of telmisartan for decreasing morning home blood pressure and pulse wave velocity in patients with mild-to-moderate hypertension (*22*).

In our study we determined the effect of the AT_1 receptor antagonist telmisartan on preactivated monocytes and its effect on monocyte adhesion in hypertensive patients after therapy.

We analyzed monocyte–endothelial cell adhesion and the expression of activity-dependent monocyte surface markers in essential hypertensive patients before and after telmisartan monotherapy for 3 months.

Methods

We administered a monotherapy of 80 mg telmisartan/day to 20 essential hypertensive patients for at least 3 months. Before the beginning of therapy and after 3 months of therapy blood samples were collected for subsequent cytometric measurement of adhesion and activity-dependent surface markers on peripheral monocytes and for isolation of monocytes and performance of adhesion assays. The monocytes were isolated by density gradient centrifugation and Dynabeads®, and adherence to human aortic endothelial cell monolayers was tested by adhesion assays.

Chemicals

All solutions and chemicals used in the isolation and activation procedures were endotoxin-free (endotoxin <0.01 ng/mL). The AT_1 receptor antagonist telmisartan was obtained from Bayer Vital (Leverkusen, Germany). If not otherwise specified, all chemicals were purchased from Sigma Chemical Co. (St. Louis, USA).

Patients

Fifteen male and five female outpatients, aged 42 to 68 years (mean age 54 years), with essential hypertension (measured before any drug administration or after they had discontinued all antihypertensive medications for at least 14 days) participated in the study. The mean body weight was 84 ± 12.5 kg and the mean body mass index was 27 ± 2.3 kg/m^2. All patients underwent routine 24-h ambulatory blood pressure measurement (ABPM) for clinical evaluation (mean blood pressure before therapy: 144/93 mmHg; mean blood pressure

after therapy: 130/84 mmHg). Exclusion criteria included renal disease, liver disease, and chronic inflammatory diseases of all sorts, including clinical evidence of atherosclerosis, elevated erythrocyte sedimentation rate, C reactive protein, leukocytosis, and cigarette smoking. Twenty healthy control subjects (mean blood pressure 125/79 mmHg, mean body weight 81 kg, mean body mass index 26 kg/m^2) were matched to patients according to age (56 years) and gender (5 women, 15 men). Written informed consent was obtained from all patients and control subjects. The protocol was approved by the local ethics committee.

Adhesion Trials

Isolation and Identification of Peripheral Blood Monocytes

Peripheral blood (100 mL) diluted with physiological salt solution containing 100 U heparin/mL was layered over Ficoll-Histopaque (Pharmacia AB, Uppsala, Sweden; specific gravity: 1.077) in tubes (LeucoSep; Greiner GmbH, Frickenhausen, Germany) for leukocyte separation and centrifuged for 30 min at 400 × *g*. Cells harvested from the interphase were washed three times in phosphate-buffered saline (PBS) (PBS-Dulbecco; Biochrom KG/Seromed, Berlin, Germany) and resuspended in PBS (containing 0.1% bovine serum albumin [BSA]).

The Dynal Monocyte Negative Isolation Kit contains Depletion Dynabeads (Dynal Biotech, Hamburg, Germany). Monocytes are negatively isolated from a mononuclear cell (MNC) sample by depletion of T cells, B cells and NK cells. Dynabeads were washed three times with PBS (containing 0.1% human serum albumin [HSA]). MNC were incubated with an antibody mixture (containing mouse monoclonal antibodies for CD2, CD7, CD16, CD19 and CD56) and blocking reagents (γ-globulin) for 10 min at 5°C. After incubation the cells were washed by adding 1 mL of PBS (containing 0.1% BSA) per 10^7 cells and centrifuged for 8 min at 500 × *g*. The supernatant was removed and the cells were resuspended and washed. Depletion Dynabeads (a secondary antibody bound to Dynabeads) were added (100 µL/10^7 mononuclear cells) to remove unwanted antibody-bound cells. The total volume for cell and bead incubation was 1 mL/10^7 cells. The cells were incubated for 15 min at 5°C. The coated cells were then separated with a magnet (Dynal MPC; Dynal Biotech) and discarded. The supernatant contained the negatively isolated monocytes.

Viability was greater than 95% as determined by trypan blue exclusion after isolation of peripheral blood monocytes. Cell viability was also determined by the propidium iodide staining method (*23*). The proportion of propidium iodide–positive cells was consistently less than 5%.

Monocytes were identified using immunofluorescence staining for cell surface antigens as described previously (*12*). The cell suspension contained > 94% monocytes. Monoclonal mouse antibodies specific for human T cells (CD3), human B cells (CD19), and human monocytes (CD14) were obtained from Becton Dickinson Biosciences GmbH (Heidelberg, Germany). An appropriate control using antibodies with an irrelevant specificity was run to determine non-specific staining. The cells stained with antibodies were analyzed for fluorescence with a fluorescence activated cell sorter (Becton Dickson Biosciences FACScalibur, San Jose, USA).

Stimulation of Isolated Monocytes

The optimal conditions and concentrations for stimulation of peripheral blood monocytes with Ang II, LPS and the AT_1 receptor antagonist telmisartan were determined by time and concentration kinetics. Peripheral blood monocytes were incubated (37°C; 5% CO_2) for 20 h at a concentration of 10^6 cells/mL in RPMI 1640 (supplemented with 10% fetal calf serum [FCS], 100 U/mL penicillin and 50 µg/mL gentamycin) either without stimulus, or with LPS (100 ng/mL) or Ang II (10^{-6} mol/L) for 30 min.

Human Aortic Endothelial Cells

Human aortic endothelial cells (HAEC) were obtained from Cambrex Bio Science (Walkersville, USA). Cells were thawed and dispensed in T-25 flasks (Nunc, Roskilde, Denmark) at 2,500 cells/cm^2 in 5 mL of endothelial growth medium 2 (EGM 2) for incubation (37°C, 5% CO_2, steam saturated atmosphere). Cells were subcultured by trypsination at 90% confluency and then seeded at a concentration of 50.000 HAEC cells in 0.5 mL EGM 2. Endothelial cells were identified immunohistochemically by direct immunofluorescent staining for von Willebrand factor (*24*).

Monocyte Adhesion Assays

The monocyte adhesion to endothelial cells was measured as described by Hahn *et al*. (*25*) with minor modifications and verified by a second adherence assay, which was carried out as previously described by McCarron *et al*. (*10*). The percent adhesion was calculated from the amount of radioactivity associated with the adherent cells divided by the total counts per min.

Flow Cytometric Analysis of Monocyte Surface Markers

For staining, 20 µL antibody solution was added to 100 µL EDTA blood, then resuspended and incubated for 20 min at 4°C. The following antibodies were used: 1) as isotype controls: mouse IgG1-FITC, IgG2a-PE, IgG2a-FITC, and IgG2b-PE; 2) for detection of surface molecules: anti-human CD14-APC, anti-human CD11b-PE, anti-human CD80-FITC, anti-human CD54-PE, anti-human CD86-FITC, anti-human CD11a-FITC, anti-human CCR5-PE, anti-human CCR1-PE and anti-human CCR2-PE. With the exception of anti-human CCR1 and CCR2 (R&D Systems GmbH, Wiesbaden, Germany), all antibodies were purchased from Becton Dickinson Biosciences GmbH. After staining, erythrocytes were lysed from whole blood by using FACS Lysing Solution

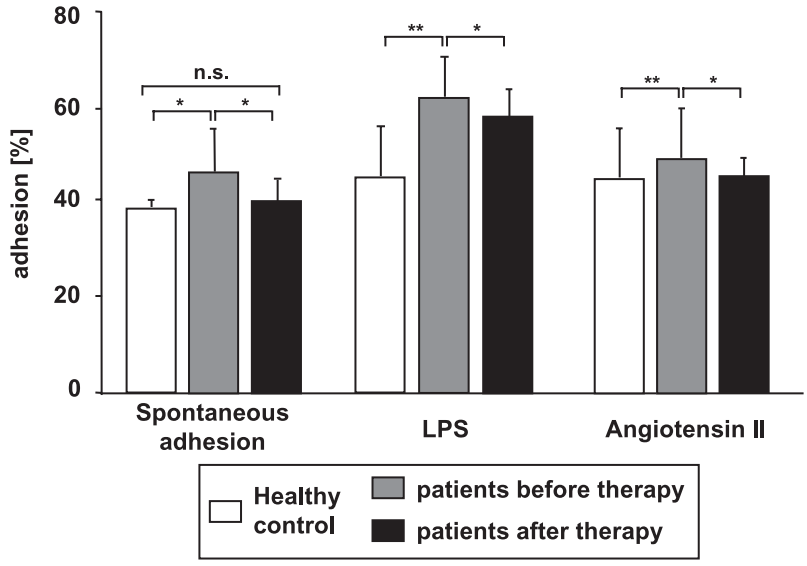

Fig. 1. *Spontaneous adhesion (mean+SD) and adhesion after LPS and angiotensin-II pretreatment of monocytes to HAEC monolayers from normotensive healthy controls and hypertensive patients before and after telmisartan therapy. *p < 0.05, **p < 0.01 by Mann-Whitney U-test; n.s., nonsignificant.*

(Becton Dickinson Biosciences GmbH) according to the manufacturer's instructions. Then, cells were washed, fixed in 1% paraformaldehyde solution and analyzed using a FACS-calibur fluorescence activated cell sorter (FACS) (Becton Dickson Biosciences). The FACS data analysis was performed by means of Cellquest software. Monocytes were identified by CD14 expression. Expression of activation markers and adhesion molecules was determined by adjusting isotype stained controls to a fixed mean fluorescence intensity (MFI) for each sample. The results are given as the MFI.

Data Analysis

Results are expressed as the mean±SD. The statistical significance of the differences was tested using the Mann-Whitney *U*-test for paired (comparison before and after therapy) or unpaired (comparison between control and hypertensive patients) samples. A *p*-value of <0.05 was considered significant. Statistical analysis was done using SPSS-software (Chicago, USA).

Results

Adhesion Assays

Activation of peripheral blood monocytes was monitored by measuring their adhesion to HAEC monolayers, which was given as the percentage of initially seeded cells, as shown in Fig. 1. The spontaneous adhesion of monocytes to HAEC monolayers from hypertensive patients before antihypertensive therapy was significantly increased compared to the monocyte adhesion of normotensive controls (46.02±9.06% *vs.* 38.69±1.78%; $p=0.017$). To determine the effect of telmisartan therapy we measured monocyte adhesion of the same hypertensive patients after a 3-month administration of telmisartan. Monocyte adhesion after telmisartan therapy was significantly decreased compared to monocyte adhesion before therapy (patients after therapy: 39.02±6.59%; $p=0.03$) and reached the levels in the normotensive controls ($p=0.583$; n.s.).

Because LPS is well established as a very potent monocyte stimulus, we determined the adhesion of isolated monocytes from hypertensive patients before and after telmisartan therapy compared with healthy, normotensive subjects as positive controls. The monocytes were activated *in vitro* by LPS treatment for 20 h. The adhesion of patient monocytes after stimulation by LPS was significantly increased compared to their spontaneous adhesion (62.76±7.01%; $p<0.01$) and compared to LPS-induced monocyte adhesion of the normotensive controls (Fig. 1). We also observed a significant decrease of LPS-induced monocyte adhesion after telmisartan therapy (58.55±4.34%, $p=0.022$; Fig. 1).

We further examined the effect of physiological stimulation with Ang II on the *in vitro* adhesion of peripheral monocytes to HAEC. The optimal concentration of Ang II for stimulation of monocytes was determined in preliminary experiments to be 10^{-6} mol/L. Ang II stimulation resulted in an increase in monocyte adhesion in normotensive and hypertensive patients compared to their spontaneous adhesion. Furthermore, Ang II–induced adhesion was significantly higher in hypertensives compared to normotensive controls (51.47±8.77%; $p<0.01$; Fig. 1) and decreased after telmisar-

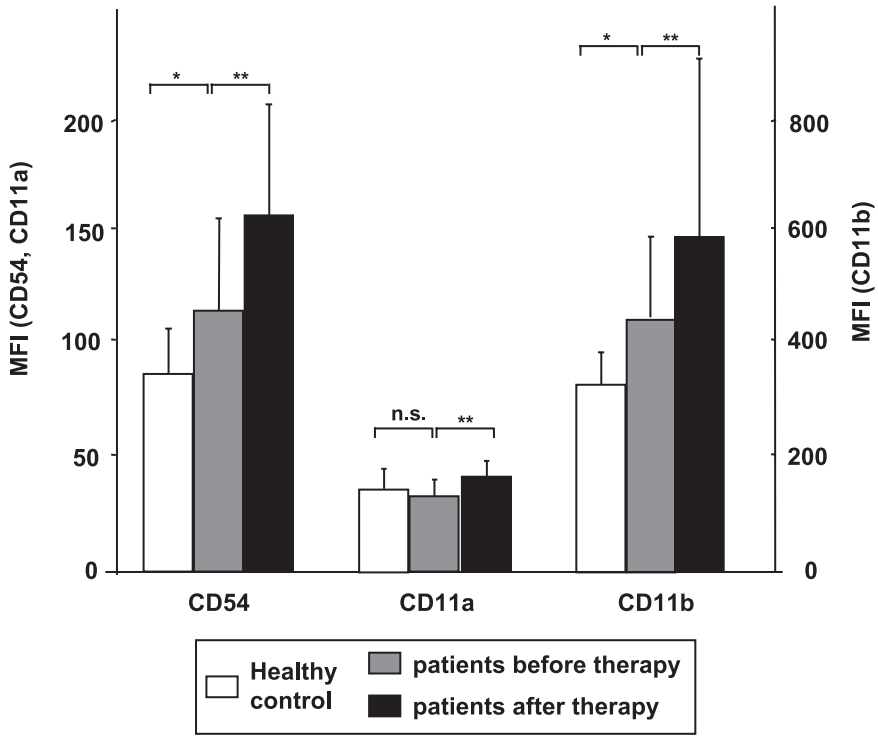

Fig. 2. *CD54, CD11a and CD11b expression (MFI) on monocytes in normotensive controls and hypertensive patients before and after telmisartan therapy. *p < 0.05, **p < 0.01 by Mann-Whitney U-test; n.s., nonsignificant.*

tan therapy (44.70±5.11%; $p=0.019$; Fig. 1).

Expression of Adhesion Molecules, Co-Stimulatory Molecules and Chemokine Receptors on Monocytes

Next, we determined the expression of adhesion molecules and chemokine receptors on monocytes in 20 hypertensive patients before and after telmisartan therapy and in 20 normotensive controls.

Expression of Adhesion Molecules CD54, CD11a and CD11b on Monocytes before and after Telmisartan Therapy

CD54 (ICAM-1), an adhesion molecule involved in intercellular adhesion, also mediates co-stimulation of T cells (*26*). CD54 is induced by LPS on monocytes (*27*), and is expressed on all CD14-positive monocytes. In hypertensive patients in the present study, the level of CD54 was significantly increased compared to that in normotensive controls (106.46±36.3 MFI *vs*. 82.93±17.5 MFI; $p=0.045$; Fig. 2). After telmisartan therapy we measured a further significant increase in CD54 expression (151.5±49.0 MFI) on the monocytes of the patients (Fig. 2).

CD11a (LFA1) is a β2-integrin and involved in the third step of the migration cascade supporting firm adhesion (*8*), and has been shown to play a role in LPS-induced adhesion of monocytes (*28*). We found expression of CD11a on all CD14+ monocytes, but there was no significant difference in CD11a expression between normotensives (33.7±10.3 MFI) and hypertensive patients (29.9±6.75 MFI; $p=0.175$). After telmisartan therapy we detected a significantly increased expression of CD11a on monocytes compared to the levels before therapy (37.23±8.3; $p=0.006$) (Fig. 2).

CD11b (Mac-1) is also a β2-integrin and is involved in adhesion of monocytes to the cytokine-activated endothelium (*29*). In the present study, the monocyte expression of CD11b was significantly increased in hypertensives compared to that in the normotensive controls (410.8±149.0 MFI *vs*. 312.4±59.8 MFI; $p=0.018$) and a further significant increase was observed after 3 months of telmisartan therapy (583.4±245.7 MFI; $p=0.007$) (Fig. 2).

Monocyte Expression of CD80 and CD86 before and after Telmisartan Therapy

CD80 and CD86 belong to the Ig-supergene family and are expressed on activated B cells, macrophages and dendritic cells. CD80 and CD86 serve as ligands for CD28, which is localized on T cells. Ligation of CD28 by CD80 and CD86 provides a major co-stimulatory signal promoting IL-2 production and proliferation of T cells (*30*). Monocytic expression of CD80 was very low and significantly decreased in hypertensive patients (1.86±0.6 MFI) compared to normotensives (2.36±0.85 MFI; $p=0.005$). After telmisartan therapy we found a significantly increased expression of CD80

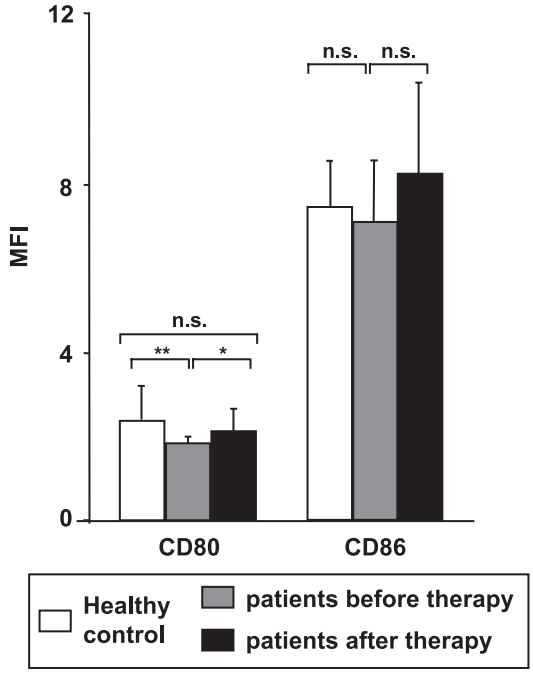

Fig. 3. *CD80 and CD86 expression (MFI) on monocytes in normotensive controls and hypertensive patients before and after telmisartan therapy. *p < 0.05, **p < 0.01 by Mann-Whitney U-test; n.s., nonsignificant.*

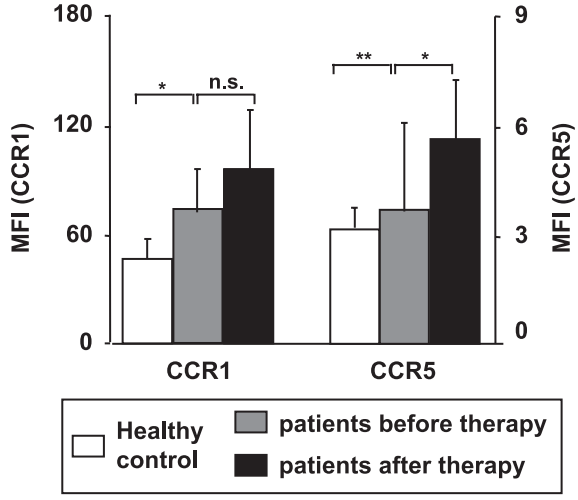

Fig. 4. *CCR1 and CCR5 expression (MFI) on monocytes in normotensive controls and hypertensive patients before and after telmisartan therapy. *p < 0.05, **p < 0.01 by Mann-Whitney U-test; n.s., nonsignificant.*

compared to the value before therapy (2.19±0.48 MFI; $p=0.02$) (Fig. 3).

Expression of CD86 on monocytes did not significantly vary between normotensive and hypertensive patients ($p=0.260$) before or after three months of telmisartan therapy (Fig. 3).

Chemokine Receptor Expression on Monocytes before and after Telmisartan Therapy

CCR1 is a G-protein–coupled receptor that preferably binds to MIP-1α, MCP-3 and 4, and Rantes (*31*). It can be expressed on monocytes, granulocytes, T cells, B cells, and dendritic cells. We observed a significantly increased monocyte expression of CCR1 in hypertensive patients compared to normal control patients (74.91±29.39 MFI *vs*. 48.6±12.47 MFI; $p=0.01$). The increase seen after telmisartan therapy did not reach the level of statistical significance (98.31±37.38 MFI; $p=0.052$) (Fig. 4).

CCR5 is also a G-protein–coupled chemokine-receptor which binds MIP-1α, MIP-1β and Rantes (*32*). Recently it was shown that deficiency of CCR5 protects against neointima formation in atherosclerosis-prone mice (*33*). We detected a very low expression of CCR5 on normotensive controls (3.06±1.04 MFI) and a significantly higher ($p=0.007$) expression in hypertensive patients (4.41±1.86 MFI). After telmisartan therapy we observed a further increase of CCR5 expression (5.57±1.73 MFI; $p=0.048$; Fig. 4).

CCR2 is a chemokine receptor that binds to MCP-1. It is widely expressed on monocytes, T cells, NK cells and dendritic cells (*31*). Recent studies suggest a critical role of CCR2 in hypertension-induced vascular inflammation (*32*). Therefore, we determined the effect of telmisartan on CCR2 expression on monocytes in a subgroup of patient before and after telmisartan therapy. As a result we found that expression of CCR2 on monocytes did not significantly vary between normotensive ($n=11$) and hypertensive patients ($n=8$; $p=0.215$) or between untreated hypertensive patients and patients receiving telmisartan monotherapy ($n=11$; 67.86±15.02 MFI *vs*. 55.15±17.00 MFI; $p=0.08$).

Discussion

The results of our present investigation showed that monocyte adhesion was elevated in patients with uncomplicated essential hypertension compared to normotensive controls. This finding is consistent with previous studies (*12*, *14*, *24*, *34*) and supports the concept that increased cellular expression of adhesion molecules in response to hypertension-related changes in endothelial structure and function constitutes a risk factors for atherosclerosis.

This concept is also supported by studies finding elevated levels of soluble circulating adhesion molecules (CAM) in subjects with essential hypertension (*35*, *36*) and with other atherosclerotic risk factors such as diabetes (*37*) and dyslipidemia (*38*).

In line with this, we found elevated expression of the adhesion molecules CD11b and CD54 and the chemokine receptors CCR1 and CCR5 on monocytes from hypertensive patients.

Fliser *et al*. showed in a prospective, double-blind, placebo-

controlled study that treatment with olmesartan significantly reduces a panel of inflammation markers that includes TNF-α and IL-6 (*39*). Our present results extend these findings. In our patients the AT_1 receptor antagonist therapy led to a significant decrease of monocyte adhesion to the human aortic endothelial monolayer. This reduced adhesion was also found after stimulation of monocytes by LPS or Ang II. This indicates the important role of AT_1 receptors for the atherogenesis and a possible benefit of telmisartan therapy for the improvement of endothelial dysfunction.

However, in contrast to the reduced functional adhesion, we observed an enhanced expression of the adhesion markers CD54 and CD11b after 3 months of telmisartan therapy. The same tendency was seen for the chemokine receptors CCR1 and CCR5. CD11a, CD80, and CD86 were downregulated in hypertensive patients compared to normotensive controls but increased after telmisartan therapy. Telmisartan seems to stimulate the expression of monocyte cell surface adhesion markers. This is also suggested by a study of Prasad *et al*., who observed enhanced L-selectin expression on monocytes after 8 weeks of losartan therapy (*40*).

Thus, reduced adhesion after telmisartan therapy cannot be attributed to reduced levels of adhesion molecule expression. As shown by our study and by other authors, Ang II enhances the adhesion of monocytes to endothelial cells. The inhibition of this enhanced adhesion by telmisartan suggests an AT_1 receptor–dependent mechanism. Kintscher *et al*. (*41*) showed that treatment of monocytes with Ang II resulted in phosphorylation of the proline-rich tyrosine kinase II (Pyk2) and of paxillin, which are both cytoskeleton-associated proteins involved in cell movement. This effect was inhibited by losartan, suggesting that the effects on the cytoskeleton of monocytes by treatment with telmisartan might control the adhesion potential of monocytes. In addition, a study by Thomas *et al*. suggests modification of actin filament function by AT_1 receptor antagonists (*42*).

Furthermore, it has recently been shown that cellular Pyk2 expression and phosphorylation are increased during hypertension and pressure overload–induced cardiac hypertrophy, suggesting a link between increased vascular pressure and cellular cytoskeletal changes (*43*, *44*). In summary, given the reported induction of Pyk2 *via* AT_1 receptor stimulation and the activated Pyk2 system in hypertension, inhibition of monocyte adhesion in hypertensive patients by the AT_1 receptor blocker telmisartan might, at least in part, be mediated *via* the regulation of cytoskeleton-associated proteins.

But how can the enhanced expression of adhesion markers on monocytes be explained? It has to be considered that Ang II exerts very diverse effects on different cell types, suggesting that multiple intracellular signalling pathways are activated by AT_1 receptor occupancy. In fact, nuclear factor-κB activation has been described and, specifically in monocytes, ERK 1/2 and p38 MAPK kinase pathways are involved in Ang II signalling and stimulation of migration (*45*). The manner in which these pathways are modulated by AT_1 receptor antagonists is not known, but besides their antagonistic effects there might be some agonistic actions remaining. Therefore, further studies are necessary to determine the association between upregulated monocyte activity markers and decreased monocyte adhesion in hypertensive patients after telmisartan therapy.

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