Telmisartan Inhibits CD4-Positive Lymphocyte Migration Independent of the Angiotensin Type 1 Receptor Via Peroxisome Proliferator-Activated Receptor-γ

Daniel Walcher, Katharina Hess, Philipp Heinz, Kerstin Petscher, Dusica Vasic, Ulrich Kintscher, Markus Clemenz, Martin Hartge, Katrin Raps, Vinzenz Hombach, Nikolaus Marx

Abstract—Migration of CD4-positive lymphocytes into the vessel wall represents an important step in early atherogenesis. Telmisartan is an angiotensin type 1 receptor (AT1R) blocker with peroxisome proliferator-activated receptor (PPAR)-γ-activating properties. The present study examined the effect of telmisartan on CD4-positive cell migration and the role of PPARγ in this context. CD4-positive lymphocytes express both the AT1R and PPARγ. Stimulation of CD4-positive lymphocytes with stromal cell-derived factor (SDF)-1 leads to a 4.1±3.1-fold increase in cell migration. Pretreatment of cells with telmisartan reduces this effect in a concentration-dependent manner to a maximal 1.6±0.7-fold induction at 10 μmol/L of telmisartan (P<0.01 compared with SDF-1-treated cells; n=22). Three different PPARγ activators, rosiglitazone, pioglitazone, and GW1929, had similar effects, whereas eprosartan, a non-PPARγ-activating AT1R blocker, did not affect chemokine-induced lymphocyte migration. Telmisartan’s effect on CD4-positive lymphocyte migration was mediated through an early inhibition of chemokine-induced phosphatidylinositol 3-kinase activity. Downstream, telmisartan inhibited F-actin formation, as well as intercellular adhesion molecule-3 translocation. Transfection of CD4-positive lymphocytes with PPARγ small interfering RNA abolished telmisartan’s effect on migration, whereas blockade of the AT1R had no such effect. Telmisartan inhibits chemokine-induced CD4-positive cell migration independent of the AT1R via PPARγ. These data provide a novel mechanism to explain how telmisartan modulates lymphocyte activation by its PPARγ-activating properties. (Hypertension. 2008;51:1-8.)

Key Words: telmisartan ■ PPARγ ■ angiotensin type 1 receptor blocker ■ CD4-positive lymphocytes ■ migration

Atherogenesis is an inflammatory process in the vessel wall involving inflammatory cells like monocytes, macrophages, and CD4-positive lymphocytes.1 In early atherogenesis, CD4-positive lymphocytes are attracted by chemotactic proteins, such as regulated upon activation, normal-T-cell expressed, and secreted (RANTES) and stromal cell-derived factor (SDF)-1 and enter the vessel wall as naïve T-helper 0 cells. In the subendothelium, these cells then encounter antigens like oxidized low-density lipoprotein and differentiate into T-helper 1 cells, subsequently releasing proinflammatory mediators like tumor necrosis factor-α and interferon-γ. These cytokines then govern the inflammatory response in the vessel wall by activating other cells, such as endothelial cells, macrophages, and vascular smooth muscle cells, thus promoting the inflammatory process in atherogenesis. It is unclear whether an inhibition of cell migration itself modulates vascular disease, but various experimental studies have shown that a reduction in CD4-positive lymphocyte recruitment hampers lesion development and plaque forma-

Received July 30, 2007; first decision August 14, 2007; revision accepted November 19, 2007.

From the Department of Internal Medicine II-Cardiology (D.W., K.H., P.H., K.P., D.V., K.R., V.H., N.M.), University of Ulm, Ulm, Germany; and the Center for Cardiovascular Research (U.K., M.C., M.H.), Institute of Pharmacology and Toxicology, Charité-Universitätsmedizin Berlin, Berlin, Germany.

Correspondence to Nikolaus Marx, Department of Internal Medicine II-Cardiology, University of Ulm, Robert-Koch-Str 8, D-89081 Ulm, Germany. E-mail nikolaus.marx@uniklinik-ulm.de

© 2007 American Heart Association, Inc.

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.107.099028
unexplored. Therefore, the current study examined the effect
of telmisartan on CD4-positive lymphocyte migration and
investigated to what extent a modulatory function of telmis-
artan on cell migration may be mediated by its PPARγ-
activating properties.

Methods

Cell Culture

Human CD4-positive lymphocytes were isolated from the freshly
drawn blood of healthy volunteers by Ficoll-Histopaque (Sigma)
gradiant centrifugation to obtain peripheral blood mononuclear
cells and subsequent negative selection of CD4-positive T cells by
magnetic bead separation (Miltenyi Biotec), as described by
the manufacturer’s protocol. The purity of CD4-positive T cells was
>97% as determined by flow cytometry.

In Vitro Cell Migration Assay

After isolation, CD4-positive cells were cultured in serum-free
medium for 16 hours. T-cell chemotaxis was assayed under serum-
free conditions in a 48-well microchemotaxis chamber (Neuro-
probe). Wells in the upper and lower chambers were separated by a
polyvinylpyrrolidone-free polycarbonate membrane (pore size: 5 μm;
Costar). CD4-positive cells at a density of 5 × 10^5/mL were
pretreated for 15 minutes with the AT1R antagonists telmisartan or
eprosartan or with the PPARγ activators rosiglitazone, pioglitazone,
or GW1929 before 3 hours of incubation with SDF-1 or RANTES
(Sigma). Migrated cells on the bottom face of the filter were stained
and counted under the light microscope. Cells were counted in 5
random high-power fields per well.

Western Blot Analysis

Standard Western blot analysis was performed using mouse anti-
human AT1R antibodies (Upstate).

Transfection of Small Interfering RNA

Specific and negative small interfering RNAs (siRNAs) were pur-
chased from Invitrogen. PPARγ siRNAs refer to PPARγ Validated
Stealth RNAi DuoPak. Negative siRNA refers to Negative Control
Validated Stealth (Invitrogen) and has no homology to any known
human gene sequence. siRNA transfection was performed using
human CD4-positive lymphocytes. Cells were isolated from blood
and incubated for 1 hour in RPMI medium 1640 with 5% human
serum. T cells were transfected with PPARγ siRNA (100 nM) using
the human T-cell nucleofector kit (Amxza Bissystems) according to
the manufacturer’s protocol. After transfection, cells were plated in
12-well plates with RPMI medium 1640 containing 5% human
serum and incubated for 48 hours. Untreated cells, amaxa nucleo-
fector solution, and negative siRNA controls were established in
parallel. To assess the role of telmisartan in mock- or PPARγ
siRNA-transfected T-cells, we used intercellular adhesion molecule
(ICAM)-3 translocation as a readout for cell migration, because both
mock- and siRNA-transfected cells no longer exhibit a full chemo-
tactic response in our chemotaxis assay (data not shown), most likely
because of the fact that the transfection procedure itself interferes
with other parts of the migration machinery.

Phosphatidylinositol Kinase Assay

After isolation, human T cells were incubated for 16 hours in RPMI
medium 1640 without serum. Cells pretreated for 15 minutes with or
without telmisartan or any other PPARγ activator were stimulated
with 100 ng/mL of SDF-1. Standard phosphatidylinositol 3-kinase
(PI3K) activity assays were performed using goat anti-human p85
(Santa Cruz) antibodies.

F-Actin Staining

CD4-positive lymphocytes (2 × 10^6 cells/mL) were treated with
SDF-1 at 100 ng/mL, for times indicated after 15 minutes pretreat-
ment with different inhibitors (telmisartan, rosiglitazone, piogli-

zone, and GW1929). After stimulation cells were fixed in 3.7%
(wt/vol) paraformaldehyde in PBS (pH 7.4) and then washed at room
temperature in Tris-buffered saline (50 mM/L of Tris-HCl [pH
7.6], 150 mM/L NaCl, and 0.1% NaN). For intracellular staining of
F-actin cells were permeabilized with 0.1% Triton X-100 for 10
minutes before application of the first antibody. Cell suspensions
were incubated for 30 minutes in PBS with fluorescein isothiocya-
nate–conjugated phallolidin (Sigma P5282). Flow cytometry analysis
was performed in a FACScan cytofluorometer (Becton Dickinson),
and induction of F-actin was measured.

ICAM3 Staining

Immunofluorescence staining was performed as described before.17
In brief, 1 to 2 × 10^6 CD4-positive lymphocytes were incubated in
special 4-well plates (Costar Corp) in a final volume of 500 μL of
complete medium on coverslips coated with collagen. Before treat-
ment with SDF-1 (100 ng/mL for 30 minutes), cells were incubated
with telmisartan, rosiglitazone, pioglitazone, or GW1929 for 15
minutes. Cells were then fixed with 3.7% (wt/vol) paraformaldehyde
in PBS (pH 7.4) at room temperature and rinsed in Tris-buffered
saline. Cells were incubated with a specific antibody against ICAM3
(mouse anti-human ICAM3, Caltag), and after washing with PBS,
carbamoylmethylidoxycyanine 3-Cy3-coupled (Dianova) goat anti-
mouse IgGs were added as secondary antibodies (dilution: 1:1000)
for 45 minutes. After washing again, slides were stained with
4’,6-diamidino-2-phenylindole (DAPI; nuclei staining). Images were
recorded with a fluorescence microscope (Leica), and cells in 5
randomly selected fields (∼100 cells) were analyzed. ICAM-3
translocation was considered to be present when a clear clustering
of ICAM3 at the uropod was visible.

Statistical Analysis

Results of the experimental studies are reported as mean±SD. Differ-
ences were analyzed by 1-way ANOVA followed by the appropriate
posthoc test. A P value <0.05 was regarded as significant.

Results

CD4-Positive Lymphocytes Express AT1 Receptors

Western blot analysis revealed that isolated human CD4-
positive lymphocytes express AT1R protein (Figure 1A). In
addition, RT-PCR demonstrated AT1 receptor mRNA
expression (data not shown).

Telmisartan Reduces CD4-Positive
Lymphocyte Migration

To examine the effect of telmisartan on CD4-positive lympho-
cyte migration, cells were stimulated with SDF-1 in the
absence or presence of telmisartan, and lymphocyte migration
was assessed in a modified Boyden chamber. SDF-1 treatment
significantly induced cell migration by 4.1±3.1-fold
(P<0.01; n=22), and pretreatment of cells with telmisartan
for 15 minutes reduced this effect in a concentration-
dependent manner to a maximal 1.6±0.7-fold induction at
10 μmol/L of telmisartan (P<0.01 compared with SDF-1
treated cells; n=22; Figure 1B). Similar effects were obtained
when RANTES was used as a stimulus to induce CD4-
positive lymphocyte migration (data not shown), suggesting that
telmisartan’s action on lymphocyte migration is indepen-
dent of the stimulus used. Treatment of cells with telmisartan
at the time of SDF-1 stimulation or treatment 15 minutes after
the addition of SDF-1 did not result in a significant reduction
of chemokine-induced cell migration (data not shown).

Next we investigated the effect of the non-PPARγ-activat-
ing AT1R antagonist eprosartan on CD4-positive lympho-
cyte migration. As shown in Figure 1C, eprosartan did not significantly influence SDF-1–induced cell migration, suggesting that telmisartan’s effect on CD4-positive cell migration may be independent of the AT1R.

**PPARγ Activators Reduce CD4-Positive Lymphocyte Migration**

Because telmisartan, a known activator of PPARγ, reduced CD4-positive lymphocyte chemotaxis, whereas the non-PPARγ-activating AT1R blocker eprosartan did not exhibit such effects, we next examined whether other well-established PPARγ activators influenced cell migration. Two PPARγ-activating TZDs, rosiglitazone and pioglitazone, significantly reduced SDF-1– (Figure 2A) and RANTES-induced CD4-positive lymphocyte migration in a concentration-dependent manner (Figure 2B). In addition, the non-TZD PPARγ activator GW1929 had similar effects (Figure 2C). These data suggest that PPARγ activation can inhibit chemokine-induced CD4-positive lymphocyte migration, potentially providing an explanation for the effects observed with telmisartan.

**Telmisartan Limits PI3K Activity in CD4-Positive Lymphocytes**

Activation of PI3K is a critical step in chemokine-induced T-cell migration downstream of the respective chemokine receptor. Therefore, we examined the effect of telmisartan on PI3K activity. As demonstrated in Figure 3A, telmisartan significantly limited SDF-1–induced PI3K activity. Moreover, rosiglitazone, pioglitazone, and GW1929 had similar effects (Figure 3B). These data suggest that telmisartan, as well as other PPARγ activators, modulates a very upstream step of the chemokine-activated signaling cascade.

**Telmisartan Reduces F-Actin Formation in CD4-Positive Lymphocytes**

Next we investigated the effect of telmisartan on F-actin formation in CD4-positive lymphocytes, a crucial mechanism in cell polarization during migration. In addition, the non-TZD PPARγ activator GW1929 significantly reduced SDF-1–induced F-actin formation, as demonstrated by flow cytometry (Figure 4A). Similarly, rosiglitazone and pioglitazone, as well as GW1929, also decreased SDF-1–induced F-actin formation (Figure 4B and 4D), but the results for pioglitazone were borderline significant.

---

**Figure 1.** A, Human CD4-positive lymphocytes express AT1Rs. Western blot analysis of isolated human CD4-positive lymphocytes and monocytes from 3 different donors. B, Telmisartan reduces SDF-1–induced CD4-positive lymphocyte migration. Human CD4-positive cells were pretreated with telmisartan (Telmi) for 15 minutes at concentrations indicated before migration experiments using SDF-1 (100 ng/mL) were performed in a modified Boyden chamber. Data are expressed as fold induction of unstimulated cells. Bars represent mean±SD (n=22); **P<0.01 vs chemokine-stimulated cells. C, Eprosartan does not affect SDF-1–induced CD4-positive cell migration. Cells were pretreated with eprosartan (Epro; 100 μM/L) or telmisartan (Telmi; 10 μM/L) for 15 minutes before migration experiments using SDF-1 (100 ng/mL) were performed. Data are expressed as fold induction of unstimulated cells. Bars represent mean±SD (n=19); **P<0.01 vs chemokine-stimulated cells.

**Figure 2.** PPARγ activators reduce CD4-positive lymphocyte migration. Human CD4-positive lymphocytes were pretreated with rosiglitazone (Rosi) or pioglitazone (Pio) for 15 minutes at concentrations indicated before migration experiments using SDF-1 (100 ng/mL; A) or RANTES (100 pg/mL; B) were performed. Data are expressed as fold inductions of unstimulated cells. Bars represent mean±SD (n=4 for SDF-1 stimulation; n=5 for RANTES stimulation); *P<0.05 vs chemokine-stimulated cells. C, Human CD4-positive lymphocytes were pretreated with the non-TZD PPARγ activator GW1929 for 15 minutes at concentrations indicated before migration experiments using SDF-1 (100 ng/mL) were performed. Data are expressed as fold inductions of unstimulated cells. Bars represent mean±SD (n=6); *P<0.05 vs chemokine-stimulated cells.
Telmisartan Inhibits ICAM3 Translocation in CD4-Positive Lymphocytes

Because ICAM3 translocation at the uropod of migrating lymphocytes is a critical step in cell movement,21 we next examined the effect of telmisartan, as well as other PPARγ activators, on ICAM3 translocation by means of immunofluorescence staining. Telmisartan, pioglitazone, and rosiglitazone, as well as GW1929, significantly diminished SDF-1–induced ICAM3 translocation (Figure 5).

Telmisartan Exhibits Its Effects on CD4-Positive Lymphocytes Independent of the AT1R via PPARγ

To investigate whether telmisartan’s actions on cell migration and ICAM3 translocation are independent of the AT1R, we pretreated human CD4-positive lymphocytes with high doses of eprosartan to block AT1Rs and then evaluated the effect of telmisartan on SDF-1–induced migration. As shown in Figure 6A, eprosartan pretreatment of cells at concentrations known to block the AT1R22 did not affect telmisartan’s inhibitory effect on SDF-1–induced migration. Similarly, blockade of the AT1R by eprosartan did not hamper the reduction of ICAM3 translocation by telmisartan, suggesting an effect of telmisartan independent of the AT1R (Figure 6B).

Finally, we examined the effect of telmisartan on SDF-1–induced ICAM3 translocation in PPARγ-negative cells as achieved by PPARγ siRNA transfection. Mock and PPARγ siRNA-transfected cells (Figure 7A) did not differ with respect to AT1R expression (Figure 7B), but in PPARγ-negative cells, telmisartan did not inhibit SDF-1–stimulated ICAM3 translocation (Figure 7C and 7D). Taken together, these data suggest that telmisartan exhibits its effects on CD4-positive lymphocyte migration and ICAM3 translocation via PPARγ.

Figure 3. Telmisartan and other PPARγ activators inhibit SDF-1–induced PI3K activity. Human CD4-positive cells were pre-treated with telmisartan (10 μmol/L; A), rosiglitazone (Rosi), pioglitazone (Pio), or GW1929 (all 5 μmol/L; B) for 15 minutes before cells were stimulated with SDF-1 (100 ng/mL). After 5 minutes, PI3K activity assay was performed. Specific dots are labeled with an arrow (PIP). Lower panels show densitometric analyses of 5 (A) or 4 (B) independent experiments. Bars represent mean±SD; *P<0.05 vs chemokine-stimulated cells.

Figure 4. PPARγ activators reduce actin polymerization in CD4–positive lymphocytes. Isolated lymphocytes were pretreated with telmisartan (n=5; A), rosiglitazone (n=4; B), pioglitazone (n=6; C), or GW1929 (n=4; D) for 15 minutes before stimulation with SDF-1. Actin polymerization was determined by flow cytometry at times indicated. Dots represent mean±SD. P values show comparison of the areas under the curve of SDF-1 vs SDF-1 and PPARγ activator-treated cells.
Discussion

The present study demonstrates that telmisartan inhibits chemokine-induced migration of CD4-positive lymphocytes by reducing PI3K activity with subsequent inhibition of F-actin formation and ICAM3 translocation. These effects of telmisartan on cell migration are mediated by PPARγ and independent of the AT1R.

CD4-positive lymphocytes express AT1R mRNA and protein as demonstrated in this study, and previous work from our group has shown the expression of PPARγ in these cells. Telmisartan is an AT1R blocker, clinically used to treat patients with hypertension, which, in addition to its effect on the AT1R, has been shown to exhibit PPARγ-activating properties. Still, previous studies only examined PPARγ-mediated metabolic effects of telmisartan, as well as effects on adipocyte differentiation and adipocyte gene expression. Our data now suggest that telmisartan exhibits PPARγ-dependent anti-inflammatory effects, as described previously for other PPARγ activators, like the antidiabetic TZDs. These drugs, in addition to their action on insulin sensitivity and glucose homeostasis, exhibit anti-inflammatory and anti-atherogenic properties in vitro and in vivo (reviewed in Reference23). As such, TZDs inhibit inflammatory activation of endothelial cells, monocyte/macrophages, and vascular smooth muscle cells, as well as CD4-positive lymphocytes. Experimental studies revealed that PPARγ-activating TZDs modulate important processes in atherogenesis, like cytokine and chemokine release, matrix metalloproteinase expression, and cell proliferation. In CD4-positive lymphocytes, PPARγ activators have been shown to limit T-helper 1 cytokine expression, suggesting a modulatory effect on inflammatory cell activation at a nodal point of lesion development. Our data now extend the current knowledge of PPARγ activator’s action in these cells by demon-

Figure 5. Telmisartan and other PPARγ activators inhibit SDF-1–induced ICAM3 translocation. A, CD4-positive lymphocytes were pretreated with telmisartan (10 μmol/L) before stimulation with SDF-1 for 30 minutes. ICAM3 translocation was assayed using immunofluorescence staining. ICAM3 translocation at the uropod of migrating cells is indicated by the arrow. Lower panel shows statistical analysis of cells positive for ICAM3 translocation as a percentage of DAPI-positive cells; bars represent mean±SD; n=5; *P<0.05 vs SDF-1–stimulated cells. B, CD4-positive lymphocytes were pretreated with rosiglitazone, pioglitazone, or GW1929 (all at 5 μmol/L) before stimulation with SDF-1. ICAM3 translocation was assayed using immunofluorescence staining. Lower panel shows statistical analysis of the percentage of ICAM3 translocation in DAPI-positive cells; bars represent mean±SD; n=5; *P<0.05 vs SDF-1–stimulated cells.

Figure 6. A, Blockade of the AT1R with eprosartan does not affect telmisartan’s effect on SDF-1–induced CD4-positive cell migration. Human CD4-positive cells were incubated with or without eprosartan (100 μmol/L; Epro) for 15 minutes and then pretreated with telmisartan (Telmi) for 15 minutes at 10 μmol/L before migration experiments using SDF-1 (100 ng/mL) were performed in a modified Boyden chamber. Data are expressed as fold induction of unstimulated cells. Bars represent mean±SD (n=5); *P<0.05 vs chemokine-stimulated cells. B, Blockade of the AT1R with eprosartan does not affect telmisartan’s effect on SDF-1–induced ICAM3 translocation. Human CD4-positive cells were treated as described in A, and ICAM3 translocation was assessed by immunofluorescence staining. ICAM3 translocation at the uropod of migrating cells is indicated by the arrow. Lower panel shows statistical analysis of cells positive for ICAM3 translocation as a percentage of DAPI-positive cells; bars represent mean±SD; n=6; *P<0.05 vs SDF-1–stimulated cells.
cytes has shown that PPARγ activators can modulate cell migration, suggesting that this pathway may be involved in the inhibition of mononuclear cell migration in general.

The telmisartan concentrations in our experiment may be higher than maximum plasma concentrations achieved in treated patients. Still, the concentrations used here correspond with the concentrations used in previous experiments investigating PPARγ-activating properties of telmisartan. In addition, telmisartan is a very lipophilic agent, and the biological action in the tissue does not necessarily correlate with plasma concentrations. Future studies are warranted to examine whether therapeutic doses of telmisartan are sufficient to modulate T-cell function in vivo.

Chemokine-induced T-cell migration is mediated by activation of G-protein–coupled receptors leading to an increase in PI3K activity with subsequent polarization of cells and formation of a leading edge and the so-called uropod in the rear. The agonists used in our study interfere with this signaling pathway by inhibiting PI3K activity. Interestingly, 15-minute pretreatment of CD4-positive cells with telmisartan or TZDs already prevented the rapid effect of SDF-1 on PI3K activation, raising the question of a nontranscriptional effect of these agents in this context, as suggested before. Previous studies in smooth muscle cells did not find such an effect of the non-PPARγ–activating AT1R antagonist losartan on PI3K activation, suggesting the possibility of an AT1R-independent action of telmisartan. Downstream of PI3K, telmisartan leads to a reduction in F-actin formation and ICAM3 translocation at the uropod of the cell, thus counterbalancing critical steps in cell movement. In addition, the effect of telmisartan and other PPARγ activators on cell migration does not depend on the chemotactic stimulus, because all substances used diminished both SDF-1- and RANTES-induced lymphocyte migration. Recent work on PPARγ-mediated effects of telmisartan has mainly focused on its metabolic action, including effects on adipocyte differentiation, expression of genes involved in insulin sensitivity, and fatty acid metabolism, as well as the modulation of glucose homeostasis. These metabolic effects of telmisartan are similar to what has been shown with PPARγ-activating TZDs. Our data now suggest that telmisartan, via PPARγ, also exhibits anti-inflammatory effects in vascular cells, as described previously for TZDs. As such, telmisartan may not only interfere with the renin-angiotensin system but may also influence vascular inflammation by its PPARγ-activating properties.

The inhibition of lymphocyte migration shown here may influence atherogenesis at a critical step. CD4-positive cells, once recruited into the subendothelial space by chemokines like SDF-1 or RANTES, differentiate to T-helper 1 cells, thus releasing proinflammatory cytokines, which then promote inflammatory activation of other cells in the vessel wall. So far, there are no data showing that an inhibition of T-cell migration directly influences atherogenesis, but various groups have demonstrated that a reduction of the expression of T-cell–specific chemokines hampers plaque formation. Thus, it may be assumed that modulating the migration of T-lymphocytes into the vasculature may also target the inflammatory process in atherogenesis at a nodal point and, as
such, address a critical step in lesion development. Still, recent data by Ait-Oufella et al have shown that a subset of CD4-positive lymphocytes, named natural regulatory cells (CD4+/CD25+ regulatory T cells), may exhibit athertoprotective effects, raising the question of whether an inhibition of CD4-lymphocyte migration may be protective under all circumstances. Therefore, future studies are warranted to determine whether such effects of telmisartan via PPARγ finally lead to a reduction in lesion size in animal models of arteriosclerosis.

**Perspectives**

Partial activation of PPARγ by selective PPARγ modulators (SPPARms) is an emerging concept designed to obtain beneficial PPARγ effects without adverse effects. PPARγ is involved in the regulation of glucose homeostasis, insulin resistance, and lipoprotein metabolism, and activators of PPARγ, like the antidiabetic TZDs rosiglitazone or pioglitazone, are in clinical use as antidiabetic agents. Furthermore, PPARγ activators have been shown to mediate anti-inflammatory effects in the vasculature. Still, in clinic, these agents do have unwanted adverse effects, like fluid retention and weight gain, underscoring the potential benefit of SPPARMs. Recent work has established that the AT1R blocker telmisartan can act as a SPPARM, thus regulating gene expression in a PPARγ-dependent manner, eg, in adipocytes. Moreover, telmisartan mediates beneficial metabolic effects in vivo. Our data suggest that telmisartan also exhibits anti-inflammatory effects in CD4-positive lymphocytes by inhibiting chemokine-induced cell migration, a critical step in arteriosogenesis. Such anti-inflammatory and antiatherogenic properties of telmisartan raise the hypothesis that SPPARMs may not only have beneficial effects in metabolic disorders, like insulin resistance and diabetes, but could also be used to modulate vascular disease. Still, future studies in animal models are needed to prove whether this concept holds true in vivo, and subsequent clinical trials are then warranted to test whether such SPPARM effects could translate into clinical benefits.

**Acknowledgments**

We thank Helga Bach, Susanne Betz, Renate Durst, and Miriam Grüb for excellent technical assistance.

**Sources of Funding**

This work was supported by grants of the Deutsche Forschungsgemeinschaft (SFB 451, project B9 and B11) to N.M. and D.W., a grant from the Landesforschungsschwerpunkt Baden-Württemberg to N.M., a grant from the Else-Kröner-Fresenius-Stiftung to D.W., and a grant of the Deutsche Diabetes Gesellschaft (Anschubförderung) to K.H. N.M. has received an unrestricted research grant from Boehringer-Ingelheim.

**Disclosures**

N.M. has received unrestricted research grants from Boehringer Ingelheim, Glaxo Smith Kline, and Takeda Pharma and has given lectures for Boehringer Ingelheim, Glaxo Smith Kline, and Takeda Pharma. U.K. has received unrestricted research grants from Boehringer Ingelheim and Glaxo Smith Kline and has given lectures for Boehringer Ingelheim, Glaxo Smith Kline, and Takeda Pharma. The remaining authors report no conflicts.

**References**


Telmisartan Inhibits CD4-Positive Lymphocyte Migration Independent of the Angiotensin Type 1 Receptor Via Peroxisome Proliferator-Activated Receptor-γ

Daniel Walcher, Katharina Hess, Philipp Heinz, Kerstin Petscher, Dusica Vasic, Ulrich Kintscher, Markus Clemenz, Martin Hartge, Katrin Raps, Vinzenz Hombach and Nikolaus Marx

Hypertension. published online December 24, 2007;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2007/12/24/HYPERTENSIONAHA.107.099028.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/