Original Article

Telmisartan Enhances Cholesterol Efflux from THP-1 Macrophages by Activating PPARγ

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Aim: The ATP binding cassette transporters A1 and G1 (ABCA1/G1) and scavenger receptor class B type 1 (SR-B1) are key molecules in cholesterol efflux and atherogenesis. These genes are regulated by peroxisome proliferator-activated receptor γ (PPARγ) and liver X receptor (LXR). Telmisartan is an angiotensin type 1 receptor blocker which has been reported to act as a ligand for PPARγ. We investigated whether PPARγ-activating ARBs affect the expression of these genes and cholesterol efflux from macrophages.

Methods and Results: Telmisartan increased ABCA1, ABCG1 and SR-B1 mRNA levels in THP-1 macrophages in a dose- and time-dependent fashion. It also increased their protein levels and enhanced apoA-I- and HDL-mediated cholesterol efflux from macrophages. The knockdown of PPARγ by siRNA abolished the telmisartan-induced expression of these genes. The knockdown of LXRα resulted in the complete and partial abolishment of telmisartan-induced ABCA1 and ABCG1 expression, respectively. We also demonstrated that telmisartan-induced SR-B1 expression was dependent on the PPARγ pathway but not on the LXRα pathway. A luciferase assay using an ABCA1 promoter construct showed that telmisartan activated ABCA1 transcription, which was abolished if the LXR binding element was mutated, indicating that increased ABCA1 transcription by telmisartan is LXR-dependent.

Conclusion: Our results showed that telmisartan enhanced both apoA-I- and HDL-mediated cholesterol efflux from macrophages by increasing ABCA1, ABCG1 and SR-B1 expression via PPARγ-dependent and LXR-dependent/independent pathways.


Key words; ARB, PPARγ, LXR

Introduction

The renin-angiotensin system plays an important role not only in the regulation of blood pressure but also in the development of atherosclerosis. After binding to their respective receptors, angiotensin II and insulin reportedly share a signal transduction pathway1). On the other hand, angiotensin II inhibits the metabo-
cade in the PPARγ and liver X receptor (LXR) pathways is important for maintaining cellular cholesterol homeostasis in macrophages\(^9, 10\) and activating PPARγ results in increased LXRα expression, which in turn transactivates the target genes\(^9, 19\). LXR and/or PPARγ reportedly up-regulated the ATP binding cassette transporters (ABC) A\(^{1}, 9, 11\), and ABCG1\(^{12, 13}\) and scavenger receptor class B type I (SR-B\(^1\))\(^14\), all of which facilitate cellular cholesterol efflux\(^12, 15-18\). The deletion of PPARγ\(^9, 19\), LXR\(^20\), ABCA1\(^21\), ABCG1\(^22\), and SR-BI\(^23\) in macrophages reportedly accelerates the development of atherosclerosis and treatment with LXR\(^24\) and PPARγ\(^25\) ligands inhibits its development; however, it is still not clear whether PPARγ-activating ARBs affect the expression of these genes and cholesterol efflux from macrophages, and regulate PPARγ-inducible genes in human cells\(^26\).

In this study, we demonstrated that telmisartan increased ABCA1, ABCG1 and SR-BI expression and enhanced apolipoprotein (apo) A-I- and high density lipoprotein (HDL)-mediated cholesterol efflux from THP-1 macrophages. The telmisartan-induced expression of these genes was regulated by PPARγ activation in both an LXRa-dependent and independent manner.

**Methods**

**Materials**

Telmisartan (Boehringer Ingelheim, Ingelheim, Germany), pioglitazone (Takeda Chemical Industries, Osaka, Japan), losartan (Cayman Chemical, Ann Arbor, MI, USA) and 22(R)-hydroxy cholesterol (22HC; Sigma, St. Louis, MO, USA) were dissolved in dimethylsulfoxide (Sigma). Human apo A-I, CD11b and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Expression data were normalized for GAPDH levels.

**Cell Culture**

THP-1 cells (Riken Cell Bank, Tokyo, Japan) were maintained in RPMI 1640 (Sigma) containing 10% fetal bovine serum (FBS). The differentiation of THP-1 monocytes into macrophages was induced in the presence of 200 nM of phorbol 12-myristate 13-acetate (PMA; Wako, Tokyo, Japan) for 72 hr. Human peripheral blood monocytes were isolated using the method of Fogelman et al.\(^{27}\) with Ficoll/Hypaque gradient centrifugation. The mononuclear cells thus obtained were re-suspended in RPMI 1640 (Sigma) supplemented with 20% autologous serum, plated onto serum-treated 10-cm dishes and incubated for 2 hr. Non-adherent cells were removed by washing three times with phosphate-buffered saline (PBS), and adherent cells were then detached by incubation in PBS containing 5% autologous serum and 0.02% EDTA at 4°C for 30 min. The adherent cells were then washed extensively and re-suspended in RPMI 1640 supplemented with 5% autologous serum. They were then plated on 10-cm dishes and incubated for 10 days so that they would differentiate into macrophages.

**Real-time Quantitative RT-PCR**

At the indicated hours after treatment with telmisartan and the other compounds, total RNA was extracted from the cells, and first-strand cDNA was synthesized from total RNA (250 ng) by placing in a Reverse Transcription Reagent (Applied Biosystems, Foster City, CA, USA)\(^28\). Quantitative PCR was performed using a Perkin-Elmer 7900 PCR machine, TaqMan PCR master mix and FAM-labeled TaqMan probes (Assays-on-Demand, Applied Biosystems) for human ABCA1, ABCG1, SR-BI, PPARγ, LXRα, LXRβ, apoE, CD11b and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Expression data were normalized for GAPDH levels.

**Western Blot Analyses**

Cells were harvested and protein extracts prepared as previously described\(^28\). They were then subjected to Western blot analyses (10% SDS-PAGE; 30 µg protein per lane) using rabbit anti-ABCA1- (Novus Biologicals, Littleton, CO, USA), ABCG1- (Novus Biologicals), SR-BI- (Novus Biologicals), mouse anti-LXRα- (PPMX, Tokyo, Japan) and β-actin (Santa Cruz, Santa Cruz, CA, USA)-specific antibodies. The proteins were visualized using a chemiluminescence method (ECL Plus Western Blotting Detection System; Amer sham Biosciences, Foster City, CA, USA).

**Determination of Cholesterol Efflux**

Cholesterol efflux experiments were performed as previously described\(^28\). After 72 hr of THP-1 monocyte differentiation into macrophages, the macrophages so produced were labeled with \[^3H\]cholesterol (1.0 µCi/mL) in RPMI 1640 containing 0.2% bovine serum albumin (BSA) for 20 hr. The cells were washed twice with PBS and incubated for 24 hr in RPMI 1640 containing 0.2% BSA plus telmisartan (20 µM), pioglitazone (10 µM) or the vehicle. The macrophages were again washed with PBS and incubated in RPMI 1640 containing 0.2% BSA in the presence and absence of apoA-I (10 µg/mL), HDL\(_2\) (50 µg/mL) or HDL\(_3\) (50 µg/mL), for 24 hr. The percentage cholesterol efflux was calculated by dividing media-derived radioactivity by the sum of the radioactivity in the media and cells.
**PPARγ Activity Assay**

PPARγ transcription factor activity was assayed using an enzyme-linked immunosorbent assay-based PPARγ transcription factor activity assay kit to detect and confirm transcription PPARγ factor activation (Active Motif, Carlsbad, CA, USA). THP-1 macrophages were treated with telmisartan, pioglitazone or vehicle for 2 hr. The cells were then rinsed, and nuclear protein was extracted according to the manufacturer’s instructions. Nuclear extracts were added to a 96-well plate that had been immobilized by an oligonucleotide containing peroxisome proliferator-response elements (5'-AAGTCAAAGGTCA-3'). After 1 hr, the wells were incubated with diluted primary PPARγ antibody to recognize the accessible epitope on PPARγ protein upon DNA binding. The horseradish peroxidase-conjugated secondary antibody was added and incubation conducted for 1 hr. At the end, the reaction was stopped, and absorbance was read at 450 nm on a spectrophotometer. This assay is specific for PPARγ activation, and there is no cross-reaction with PPARα or PPARβ.

**siRNA-mediated Macrophage RNA Interference**

Human PPARγ- and LXRα-specific small interfering RNA (siRNA) and scrambled control RNA oligonucleotides were purchased from Ambion Inc. (Austin, TX, USA). The transfection of siRNA was performed using TransIT-TKO Transfection Reagent according to the manufacturer’s instructions (Mirus Bio Corporation, Madison, WI, USA). Briefly, 40 nM of scrambled control RNA oligonucleotide or either PPARγ-siRNA or LXRα-siRNA were added to THP-1 cells 48 hr after treatment with PMA for differentiation. The cells were incubated for a further 24 hr, washed and then the indicated doses of telmisartan and pioglitazone were added. The cells were harvested 24 hr later and mRNA levels determined using RT-PCR. The oligonucleotide sequences used to construct siRNA used in this study were: 5'-GGUUGAACACCCUUGCAUCCtrs-3' and 5'-GGUUGAACACCCUUGCAUCCtrs-3' for PPARγ (PPARγ-siRNA); and 5'-UUGUGUGACUGAAT-3' and 5'-UUUGUGUGACUGAAT-3' for LXRα (LXRα-siRNA).

**Construction of Luciferase Reporter Plasmids, DNA Transfection and Luciferase Assays**

Luciferase reporter plasmids, ABCA1-Luc and ABCA1-Luc DR4mut, which respectively contain the human ABCA1 promoter region spanning ~940 to +110 bp with or without mutations in direct repeat 4 (DR4), were constructed as previously described28.

Forty-eight hr after treatment with PMA, THP-1 cells were transfected with 1.8 μg of ABCA1-Luc or ABCA1-Luc DR4mut and 0.1 μg of phRL-TK (Promega) per well using the TransIT-TKO Transfection Reagent. Twenty-four hr after transfection, the media were replaced with RPMI 1640 containing 5% FBS, with or without the indicated doses of telmisartan, pioglitazone or 22HC, and incubated for an additional 24 hr. Luciferase assays were performed as previously described28.

**Statistical Analysis**

ANOVA and the Mann-Whitney U test were performed for statistical analysis as appropriate. Statistical significance was designated at \( p < 0.05 \). Values are expressed as the mean ± SEM.

**Results**

**Telmisartan Induces ABCA1, ABCG1, SR-B1 and LXRα Gene Expression**

Twenty-four hr after treatment with telmisartan, ABCA1, ABCG1, SR-B1 and LXRα mRNA levels in THP-1 macrophages had increased in a dose-dependent manner (1-20 μM, \( C_{\text{max}} \) 1.8 ± 1.1 μM) after administration of telmisartan 80 mg to healthy subjects20, and similar changes were noted in response to treatment with the PPARγ ligand, pioglitazone (Fig. 1A). The other ARB, losartan, had no significant effect on expression of these genes, suggesting that telmisartan increased their expression independently of its AT1R blocking action (Fig. 1A). Fig. 1B shows that telmisartan produced a marked increase in SR-B1 and LXRα mRNA levels up to 8 hr after treatment, but the real increases in ABCA1 and ABCG1 mRNA levels came after 8 hr and continued after 16 hr. In contrast, there was a decrease in PPARγ mRNA levels up to 16 hr which continued to be low thereafter.

We also observed that 10 μM of telmisartan significantly increased ABCA1, ABCG1, SR-B1 and LXRα mRNA levels in human monocyte-derived macrophages (Fig. 2), and that telmisartan and pioglitazone increased PPARγ transcription factor activity, using an enzyme-linked immunosorbent assay-based PPARγ transcription factor activity assay kit (Fig. 3). There was no change in LXRβ mRNA levels after treatment with telmisartan or the other compounds (data not shown).

**Telmisartan Increases ABCA1, ABCG1 and SR-B1 Protein Levels and Cholesterol Efflux from THP-1 Macrophages**

Having established that telmisartan increased ABCA1, ABCG1, SR-B1 and LXRα mRNA levels, we
Fig. 1. Telmisartan increases ABCA1, ABCG1, SR-BI and LXRα, and attenuates PPARγ gene expression in THP-1 macrophages.

THP-1 macrophages were treated with the vehicle (Cont) or the indicated concentrations of telmisartan (Tel), losartan (Los), or pioglitazone (Pio) for 24 hr (A) or indicated hours (B). Real-time quantitative RT-PCR was performed as described in Methods. The mRNA levels of each gene were standardized for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) levels. The results from 3 separately performed experiments are expressed relative to the controls and presented as the mean ± SEM. *p<0.05 vs control.

Fig. 2. Effects of telmisartan and pioglitazone on ABCA1/G1, LXRα and SR-BI mRNA levels in human monocyte derived macrophages (HMDM).

HMDM were treated with 20 μM of telmisartan, 10 μM of pioglitazone or vehicle for 24 hr. Total RNA was extracted and real-time quantitative RT-PCR was performed as described in Materials and Methods to determine ABCA1 mRNA expression levels. The relative ABCA1 mRNA abundance was calculated by dividing the values for the expression levels of ABCA1 by those for GAPDH. The results for 3 samples are presented as the mean ± SE. *p<0.05 versus control. P values were calculated using Mann-Whitney’s U test.

Fig. 3. Telmisartan enhances PPARγ transcriptional activity.

THP-1 macrophages were treated with 20 μM telmisartan, 10 μM pioglitazone or vehicle for 24 hr. The preparation of nuclear extracts and the measurement of PPARγ transcription activity were performed as described in Materials and Methods. The results for 3 samples are presented as the mean ± SE. *p<0.05 versus control. P values were calculated using Mann-Whitney’s U test.
examined its effect on the protein levels of these molecules and cholesterol efflux from THP-1 macrophages. Both telmisartan and pioglitazone increased ABCA1, ABCG1, SR-B1 and LXRα protein levels and this was consistent with the increases in mRNA levels observed (Fig. 4A). Mirroring the increases in the protein levels of ABCA1, ABCG1 and SR-B1 they brought about, telmisartan and pioglitazone significantly increased the cholesterol efflux mediated by both apoA-I and HDL (Fig. 4B).

PPARγ- and LXRα- siRNA Attenuate the Stimulatory Effect of Telmisartan on ABCA1, ABCG1 and SR-B1 mRNA Levels

We used the siRNA approach to determine whether the telmisartan-induced expression of ABCA1, ABCG1 and SR-B1 is dependent on PPARγ and/or LXRα. PPARγ- and LXRα-siRNA suppressed PPARγ and LXRα mRNA levels by up to 75% and up to 91%, respectively (Fig. 5A and 5C). In these experiments, transient transfection of THP-1 macrophages with PPARγ-siRNA substantially abolished telmisartan-mediated induction of ABCA1, ABCG1, SR-B1 and LXRα expression (Fig. 5B). Nonsilencing, scrambled siRNA had no effect. LXRα-siRNA also abolished the increase in ABCA1 mRNA levels brought about by telmisartan (Fig. 5D); however, it only reduced telmisartan-induced ABCG1 expression by up to 20% and had no effect on the increase in SR-B1 mRNA levels induced by telmisartan (Fig. 5D). These findings suggest that telmisartan-induced ABCA1 and ABCG1 expression is mediated by PPARγ, and that the effect of telmisartan on ABCA1 and ABCG1 is completely and partially dependent on LXRα, respectively. Furthermore, it seems that the increase in SR-B1 expression due to telmisartan is dependent on PPARγ, but not LXRα.

Increase in ABCA1 Gene Expression Induced by Telmisartan is Associated with LXR-Dependent Transcriptional Activation

To investigate the effect of telmisartan on ABCA1 promoter activity, ABCA1-Luc was transfected into THP-1 macrophages and a luciferase assay was performed (Fig. 6) in experiments in which telmisartan, pioglitazone and an LXR ligand, 22HC, were added. Telmisartan increased ABCA1 promoter activity in pace with the increase in mRNA levels it brought about (Fig. 6B). Pioglitazone and 22HC also enhanced transcription of the ABCA1 reporter gene.

It has been reported that LXRαs form heterodimers with retinoid X receptor (RXR) and bind to conserved consensus cis-element, DR4, in the ABCA1 promoter region, resulting in the activation of transcrip-
When the DR4 mutant-containing reporter vector (ABCA1-Luc DR4mut, Fig. 6A) was used, telmisartan had no effect on ABCA1 promoter activity, and neither did pioglitazone or 22HC (Fig. 6B), indicating that telmisartan-activated ABCA1 transcription is dependent on LXR.

**Discussion**

Our observations suggest that the effect of telmisartan on the expression of ABCA1, ABCG1, SR-BI and LXRα is mediated by PPARγ activation, and not by AT1R blockade. Schupp et al.\(^{30}\) observed that typical PPARγ ligands and the individual PPARγ-activating ARBs, telmisartan and irbesartan, brought about distinct conformational changes in PPARγ, which were associated with selective cofactor recruitment and a distinctive gene expression profile, in murine adipocytes. They also demonstrated that pioglitazone and telmisartan differentially regulate ABCA1 (do not change and decrease, respectively) and ABCG1 (decrease and do not change, respectively) expressions in 3T3-L1 adipocytes using DNA microarrays. The discrepancy between their observations and our findings could be due to species- and/or cell-specific regulation of these genes including distinct cofactors involved in the transcriptional machinery. The present study demonstrated telmisartan’s PPARγ-activating effects in human cells for the first time\(^ {26}\), and that telmisartan stimulates the PPARγ-LXRα pathway, resulting in ABCA1/G1 activation, effects which have not been observed in murine adipocytes\(^ {30}\).

The experiments using siRNAs with the objective of suppressing PPARγ or LXRα expression indicated that telmisartan and pioglitazone were almost completely mediated via the PPARγ-LXRα pathway. Also, in the assays to measure promoter activity, we found that the increase in ABCA1 mRNA levels due to telmisartan and pioglitazone was not observed when DR4 was mutated. Furthermore, a recent study\(^ {13}\) noted that a PPARγ agonist had a stimulatory effect on ABCA1.
indicate that activated PPARα/β macrophages, suggesting that the activation of PPARα between wild-type and LXRα knockdown on ABCG1. As it is still not clear whether this LXR-independent effect is mediated by PPARγ directly or by other pathways affected by PPARγ, we are currently conducting further studies to determine whether ABCG1 is transcriptionally regulated by PPARγ.

The present study suggests that both pioglitazone- and telmisartan-mediated induction of SR-B1 mRNA expression are independent of the LXR pathway. We also found that an LXR agonist brought about no changes in SR-B1 mRNA levels in macrophages (data not shown). Recently, other researchers have demonstrated that SR-B1 expression in atherosclerotic lesion macrophages is regulated by PPARγ[14] and activated PPARγ transcriptionally stimulates hepatic SR-B1 expression[15]. The SR-B1 expression in macrophages induced by pioglitazone and telmisartan in our study could be due to a similar mechanism.

The changes in ABCA1, ABCG1, SR-B1 and LXRα levels with time following treatment with telmisartan suggest that SR-B1 is directly up-regulated by telmisartan-mediated PPARγ and, in the case of ABCA1, telmisartan first activates LXRα, which then induces ABCA1 transcription, consistent with the results obtained in siRNA experiments. The results of these experiments indicate that the newly produced proteins induced by PPARγ and/or activated PPARγ could be involved to a major extent in increased ABCG1 expression due to telmisartan, and those induced by LXRα might only be partly involved.

Interestingly, telmisartan and pioglitazone down-regulated PPARγ mRNA levels in THP-1 macrophages in our study. These observations are similar to the findings of Schupp et al.[20] who showed that PPARγ mRNA levels were down-regulated after incubation with telmisartan and pioglitazone in murine adipocytes. Since the mechanism for this negative regulation of PPARγ expression by its ligands is still unclear, further study is necessary.

Our data show that telmisartan enhanced both apoA-I- and HDL-mediated cholesterol efflux, and increased ABCA1, ABCG1 and SR-B1 protein levels, which was consistent with changes in mRNA levels. It has been reported that lipid-poor apoA-I contributes to ABCA1-mediated cholesterol efflux from cells, but not HDL[15, 16]. On the other hand, ABCA1 has been reported to promote cholesterol efflux to HDL, but not to apoA-I[16, 17]. SR-B1 is also known to promote HDL-mediated cellular cholesterol efflux[18]. Further, recent research has demonstrated that the deletion of ABCA1[21], ABCG1[22], and SR-B1[23] in macrophages

expression in wild-type macrophages but not on LXRα/β double knockout macrophages. These findings indicate that activated PPARγ increases ABCA1 mRNA levels at the transcriptional level in an LXR-dependent manner.

After treatment with LXRα-siRNA, we noted that telmisartan-induced ABCA1 expression was substantially blocked whereas ABCG1 expression was only partially blocked. In contrast, ABCG1 expression was completely suppressed by PPARγ-siRNA. In this regard, Li et al.[13] reported no difference in the stimulatory effect of PPARγ agonists on ABCG1 expression between wild-type and LXRα/LXRβ double knockout macrophages, suggesting that the activation of PPARγ-induced ABCG1 expression is independent of LXR. On the other hand, Laffitte et al.[31] reported that LXR agonist-induced ABCA1 and ABCG1 expressions in macrophages were completely abolished by the deletion of both LXRα and LXRβ. Other studies have shown that the ABCG1 gene is transcriptionally activated by activated LXR through its binding elements[32]. Taken together, the above observations suggest that ABCG1 is regulated via PPARγ, both in an LXRα-dependent and -independent manner, and the LXRα-independent effect of PPARγ activation on ABCG1 expression could overwhelm the inhibitory effect of LXRα knockdown on ABCG1. As it is still not clear whether this LXR-independent effect is mediated by PPARγ directly or by other pathways affected by PPARγ, we are currently conducting further studies to determine whether ABCG1 is transcriptionally regulated by PPARγ.

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The changes in ABCA1, ABCG1, SR-B1 and LXRα levels with time following treatment with telmisartan suggest that SR-B1 is directly up-regulated by telmisartan-mediated PPARγ and, in the case of ABCA1, telmisartan first activates LXRα, which then induces ABCA1 transcription, consistent with the results obtained in siRNA experiments. The results of these experiments indicate that the newly produced proteins induced by PPARγ and/or activated PPARγ could be involved to a major extent in increased ABCG1 expression due to telmisartan, and those induced by LXRα might only be partly involved.

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results in increased atherogenesis. Telmisartan has already been observed to have an anti-atherosclerotic effect in a study using monkeys and all of the above evidence suggests that in this effect, there could be a contribution from its ability to enhance cholesterol efflux from macrophages. Regarding ABCG1, recent studies have reported a decrease in atherosclerosis in mice transplanted with ABCG1-knockout bone marrow, however, no study has demonstrated the effect of ABCG1 overexpression in macrophages on the development of atherosclerosis. Therefore, further studies are needed to assess whether increased cholesterol efflux from macrophages due to telmisartan-induced ABCG1 expression contributes to the development of atherosclerosis.

There is accumulating evidence showing that PPARγ-activating ARBs bring about favorable changes in glucose and lipid metabolism. The combination of this effect and their antihypertensive action could help attenuate the development of atherosclerotic diseases. The present study demonstrates that PPARγ activation by telmisartan is part of a novel pathway having possibilities for atherogenesis prevention, in which cholesterol efflux from macrophages is increased, and ABCA1, ABCG1 and SR-BI expressions are enhanced. Clinical studies are now needed to investigate whether PPARγ-activating ARBs would be superior to non-PPARγ-activating ARBs in terms of preventing atherosclerotic diseases.

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