Suppression of Ocular Inflammation in Endotoxin-Induced Uveitis by Blocking the Angiotensin II Type 1 Receptor

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PURPOSE. To examine whether the angiotensin II type 1 receptor (AT1-R) signaling plays a role in ocular inflammation in endotoxin-induced uveitis (EIU).

METHODS. EIU was induced in C57BL/6 mice by a single intraperitoneal injection of 150 μg lipopolysaccharide (LPS). Tissue localization, mRNA expression, and protein levels of AT1-R in murine retinas were examined by immunohistochrometry, RT-PCR, and Western blot analyses, respectively. Telmisartan, an AT1-R antagonist widely used as an antihypertensive agent, was administered intraperitoneally at a dose of 10 mg/kg daily for 5 days until the injection of LPS. Twenty-four hours after administration, leukocyte adhesion to the retinal vasculature was evaluated with a concanavalin A lectin perfusion-labeling technique. Retinal mRNA and protein levels of intercellular adhesion molecule (ICAM)-1 were examined by RT-PCR and ELISA, respectively. Protein concentration and inflammatory cells in the aqueous humor were also measured.

RESULTS. Retinal vessels were positive for AT1-R. In mice with EIU, retinal AT1-R mRNA and protein levels were significantly increased when compared to the normal control. EIU animals also showed significant increases in the number of inflammatory cells infiltrating the anterior chamber and adhering to the retinal vessels and in retinal ICAM-1 levels. Administration of telmisartan to EIU mice resulted in significant suppression of retinal ICAM-1 expression and leukocyte adhesion and infiltration compared with vehicle treatment. Protein concentration in the aqueous humor of telmisartan-treated EIU mice tended to be lower than that of vehicle-treated EIU mice, but the difference was not statistically significant.

CONCLUSIONS. AT1-R signaling blockade inhibited retinal ICAM-1 upregulation and leukocyte adhesion and infiltration in the EIU model. These results suggest the potential use of an AT1-R antagonist as a therapeutic agent to reduce ocular inflammation.

Endotoxin-induced uveitis (EIU) is an animal model of acute ocular inflammation induced by the administration of lipopolysaccharide (LPS), a component of Gram-negative bacterial outer membranes.1-3 Because uveitis frequently leads to severe vision loss and blindness with retinal vasculitis, retinal detachment, and glaucoma, it is important to elucidate further the mechanisms in the development of ocular inflammation. LPS enhances the expression of various inflammatory mediators, such as interleukin (IL)-6,5,6 tumor necrosis factor (TNF)-α,5 prostaglandin E2,6 and monocyte chemotactic protein (MCP)-1,7 as well as the production of nitric oxide,6 all of which contribute to the development of EIU, resulting in the breakdown of the blood-ocular barrier and in the infiltration of leukocytes. For the first phase of leukocyte infiltration, cell adhesion to vascular endothelium is essential, in which adhesion molecules play major roles.8 Among various adhesion molecules, intercellular adhesion molecule (ICAM)-1 and its receptor, lymphocyte function-associated antigen (LFA)-1, are necessary for the development of EIU.9-10 Although EIU was originally used as a model of anterior uveitis, increasing evidence shows that it also involves inflammation in the posterior segment of the eye with recruitment of leukocytes that adhere to the retinal vasculature and infiltrate the vitreous cavity.11,12

The renin-angiotensin system is a major controller of systemic blood pressure. Angiotensin II, the effector molecule of the system, has two cognate receptors: angiotensin II type 1 receptor (AT1-R) and AT2-R.13,14 Because major functions of angiotensin II are mediated by AT1-R, its antagonists are widely used to treat patients with hypertension and cardiovascular diseases. Recently, several studies have demonstrated the diverse biological functions of angiotensin II as a modulator of angiogenesis, vascular remodeling, and inflammation.15-20 As an inflammatory mediator, angiotensin II enhances vascular permeability through prostaglandins and vascular endothelial growth factor,17 and contributes to the recruitment of inflammatory cells by inducing chemokines and adhesion molecules.18,19 Moreover, angiotensin II directly induces the proliferation and differentiation of inflammatory cells per se.20 AT1-R blockade is reported to attenuate such inflammatory processes effectively.15-19 Recent studies have demonstrated the prevention of EIU by suppressing inflammatory mediators including IL-6, TNF-α, cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), and MCP-1.1,3,4,7,21-24 However, it is not clear whether AT1-R blockade is effective in reducing ocular inflammation. In the current study we show for the first time the anti-inflammatory effects of an AT1-R antagonist, telmisartan, on ocular inflammation in a murine model of EIU.

METHODS

Animals and Induction of EIU

C57BL/6 mice (7-10 weeks old; SLC, Shizuoka, Japan) were used. All animal experiments were conducted in accordance with the ARVO

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Statement for the Use of Animals in Ophthalmic and Vision Research. The ethics committee of our institution approved all surgical interventions and animal care procedures, which were in accordance with the Guidelines and Policies for Animal Surgery provided by the Animal Study Committees of the Central Institute for Experimental Animals of Keio University. Animals received a single intraperitoneal injection of 0.15 mg LPS from Escherichia coli (Sigma-Aldrich, St. Louis, MO) in 0.15 mL phosphate-buffered saline (PBS).

**Pretreatment with Telmisartan**

Telmisartan was a gift of Boehringer Ingelheim, Ingleheim, Germany. Animals were pretreated with 0.15 mL intraperitoneal injections of vehicle (0.25% dimethylsulfoxide [DMSO] in PBS) or telmisartan daily for 5 days until the injection of LPS. LPS was injected immediately after the fifth telmisartan injection. We dissolved the telmisartan in 30 mM DMSO, diluted to 60 μM with PBS and injected into mice at a dose of 10 mg/kg body weight. This dose was sufficient to block AT1-R signaling to decrease systemic blood pressure in rats.25 The effects of telmisartan pretreatment on ocular inflammation were evaluated 24 hours after LPS injection.

**Lectin Labeling of Retinal Vasculature and Adherent Leukocytes**

The retina-adherent leukocytes were imaged by perfusion labeling with fluorescent-isothiocyanate (FITC)-coupled concanavalin A lectin (con A; Vector, Burlingame, CA), as described previously.26 In mice under deep anesthesia, the chest cavity was opened and a 27-gauge needle was introduced into the left ventricle. After injection of 2 mL of PBS to remove erythrocytes and nonadherent leukocytes, 2 mL FITC-conjugated con A lectin was perfused. After the eyes were enucleated, the retinas were flattened. The flatmounts were imaged with an epifluorescence microscope (IX71; Olympus, Tokyo, Japan), and the total number of con A-stained adherent leukocytes per retina was determined.

**Immunohistochemistry for AT1-R**

Immunohistochemical experiments were performed with the murine eyes. For histopathologic evaluation, the specimen was fixed with 4% paraformaldehyde (PFA) at 4°C immediately after removal and embedded in paraffin. Three-micrometer paraffin sections were incubated overnight at 4°C with a rabbit polyclonal antibody against human AT1-R (Santa Cruz Biotechnology, Santa Cruz, CA) at a 1:100 dilution. After incubation, they were reacted for 30 minutes at room temperature with goat antibodies against rabbit immunoglobulins (IgGs) conjugated to a peroxidase-labeled dextran polymer (En Vision + rabbit; Dako Corp., Carpinteria, CA). As a negative control for staining, the first antibodies were replaced with nonimmune rabbit IgGs (Dako).

Color was developed with DAB (3,3′-diaminobenzidine tetrahydrochloride; 0.2 mg/mL; Dojindo Laboratories, Kumamoto, Japan) in 0.05 M Tris-HCl (pH 7.6) containing 0.003% hydrogen peroxide, and the sections were counterstained with hematoxylin.

**Aqueous Humor Analyses**

Aqueous humor was collected by anterior chamber puncture with a 30-gauge needle at 0, 6, 12, 24, and 48 hours after LPS injection in vehicle- and telmisartan-treated EIU mice. Protein concentration was determined with a protein quantification kit (Dojindo Laboratories), and absorbance was measured with a microplate reader (Bio-Rad Laboratories, Hercules, CA). For evaluation of inflammatory cells in the anterior chamber, 1 μL of aqueous-humor samples were dropped on a polystyrene-coated slide (Sigma-Aldrich) and air dried. Slides were processed with Wright’s stain, and the total number of cells in each drop was counted under a light microscope, as described previously.27

**RT-PCR Analyses**

Total RNA was isolated from the retina and the iris-ciliary body complex with extraction reagent (TRIzol; Invitrogen, Carlsbad, CA) and reverse-transcribed with a cDNA synthesis kit (First-Strand; Amersham Biosciences, Inc., Piscataway, NJ) according to the manufacturer’s protocols. PCR was performed with Taq DNA polymerase (Toyobo, Tokyo, Japan) in a thermal controller (MiniCycler; MJ Research, Watertown, MA). The primer sequences were as follows: 5′-ATG TGG CAC CAC ACC TTC TAC AAT GAG CTG CG-3′ (sense) and 5′-CGT CAT ACT CCT GCT GCT TGC TGA TCC ACA TCT GC-5′ (antisense; 837 bp) for β-actin; 5′-TCA CCT GCA TCA TCA GCT GG-3′ (sense) and 5′-AGC TGG TAA GAA TGA TTA GG-3′ (antisense; 204 bp) for mouse AT1-R; 5′-GTG TGC AGC TTT GGG AGT GTA-3′ (sense) and 5′-CTG GCC TGG GAG ACT CAG TG-5′ (antisense; 505 bp) for ICAM-1; 5′-TTC TTC GCT GCA AGA GAC T-3′ (sense) and 5′-TGT ATG CTC TGT CAG AAG GAC T-3′ (antisense; 430 bp) for IL-6; 5′-AGG CCA CAG AGT AGG AAA CCA CCA A-3′ (sense) and 5′-ACA CCC ATT CCC TTC ACA GAG CAA T-3′ (antisense; 446 bp) for TNF-α; 5′-ATG AGC TTG CTG TGG TAT CTA TCA A-3′ (sense) and 5′-CAC TAA GAC AGG CCC TTC ATC CAC A-3′ (antisense; 449 bp) for COX-2; 5′-TCA CGC TGT GGT CTT GTC CAC T-3′ (sense) and 5′-TTG TCT CTG GGT CTT CTG A-3′ (antisense; 472 bp) for iNOS; and 5′-ATC CCA ATG AGT AGG CAG GAG AG-3′ (sense) and 5′-CAG AAG TGC TTG AGG TGG TTG TG-5′ (antisense; 617 bp) for MCP-1.

**Western Blot Analysis for AT1-R**

The animals were killed with an overdose of anesthesia, and the eyes were immediately enucleated. The retina and the iris-ciliary body complex were carefully isolated and placed into 200 μL of lysis buffer (0.02 M HEPES, 10% glycerol, 10 mM Na4P2O7, 100 μM Na3VO4, 1% Triton, 100 mM NaF, and 4 mM EDTA [pH 8.0]) supplemented with protease inhibitors (2 mg/L aprotinin, 100 μg/ml phenylmethylsulfonyl fluoride, 10 μg/ml leupeptin, and 2.5 μg/ml pepstatin A) and sonicated. The lysate was centrifuged at 15,000 rpm for 15 minutes at 4°C, and the supernatants were collected and mixed with sample buffer. Each sample containing 50 μg of total protein was then boiled for 5 minutes, separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis SDS-PAGE, and electroblotted to polyvinylidene fluoride (PVDF) membrane (Millipore Corp., Bedford, MA). After nonspecific binding was blocked with 5% bovine serum albumin, the membranes were incubated with a rabbit anti-human AT1-R polyclonal antibody (1:100, Santa Cruz Biotechnology) at room temperature for 1 hour, followed by incubation with a horseradish-peroxidase-conjugated goat antibody directed against rabbit IgGs (1:5000; BioSource, Camarillo, CA). The signals were visualized with an enhanced chemiluminescence kit (ECL; Amersham Biosciences, Inc.) according to the manufacturer’s protocol.

**Enzyme-Linked Immunosorbent Assay for ICAM-1**

The animals were killed with an overdose of anesthesia, and the eyes were immediately enucleated. The retina was carefully isolated and placed into 200 μL of lysis buffer supplemented with protease inhibitors and sonicated. The lysate was centrifuged at 15,000 rpm for 15 minutes at 4°C, and the ICAM-1 level in the supernatant was determined with the mouse ICAM-1 kit (R&D Systems Inc., Minneapolis, MN) according to the manufacturer’s protocol. The tissue sample concentration was calculated from a standard curve and corrected for protein concentration.

**Morphometric and Statistical Analyses**

All results are expressed as the mean ± SD. The number of leukocytes in each flatmount was counted independently by two investigators with the epifluorescence microscope. The data were processed for statistical analyses (Mann-Whitney test). Differences were considered to be statistically significant at P < 0.05.
Effects of AT-1 Blockade on Ocular Inflammation

**RESULTS**

**AT1-R Tissue Localization and Upregulation in EIU**

Immunohistochemistry for AT1-R was performed to identify its expression in the eyes in normal (Figs. 1A, 1C) and EIU (Figs. 1B, 1D) mice. AT1-R immunoreactivity was detected mainly on the endothelial cells of inner retinal vessels (Figs. 1A, 1B) and nonpigmented epithelial cells of the ciliary body (Figs. 1C, 1D). Retinas and iris–ciliary body complex were subjected to RT-PCR and Western blot analyses to detect the expression of AT1-R at mRNA (Fig. 1E) and protein (Figs. 1F, 1G) levels, respectively. AT1-R mRNA and protein levels of the retina and the iris–ciliary body complex in EIU mice were significantly higher than in normal, age-matched animals.

**Effects of Telmisartan on Retinal Leukocyte Adhesion**

The retina-adherent leukocytes were imaged by perfusion labeling with FITC-coupled con A. Leukocyte counts were evaluated in the posterior retina around the optic disc (Figs. 2A–D), the midperipheral retina near the equator of the globe (Figs. 2E–H), and the peripheral (anterior) retina next to the ora serrata (Figs. 2I–L). Retina-adherent leukocytes, which were few in normal mice (Figs. 2A, 2E, 2I), increased with induction of EIU (Figs. 2B, 2F, 2J). Compared with vehicle-treated EIU retina (Figs. 2C, 2G, 2K), telmisartan administration (Figs. 2D, 2H, 2L) suppressed leukocyte adhesion in the EIU retina. The total number of adherent leukocytes in nontreated EIU mice (125.3 ± 30.5) was significantly (P < 0.01) higher than in normal age-matched control animals (4.4 ± 2.1). Telmisartan-treated EIU mice showed a significant (P < 0.01) decrease in leukocyte counts (to 62.5 ± 12.0), compared with vehicle-treated EIU mice (to 116.0 ± 20.1) or nontreated EIU mice (to 125.3 ± 30.5) (Fig. 2M).

**Effects of Telmisartan on Retinal ICAM-1 Expression**

Retinal ICAM-1 expression at mRNA and protein levels was analyzed by RT-PCR (Fig. 3A) and ELISA (Fig. 3B), respectively. Retinal ICAM-1 mRNA expression in nontreated and vehicle-treated EIU mice was higher than in normal age-matched control animals. Systemic administration of telmisartan substantially reduced ICAM-1 mRNA expression (Fig. 3A). Similarly, retinal ICAM-1 protein levels were significantly attenuated after pretreatment with telmisartan (P < 0.05, Fig. 3B).

**Effects of Telmisartan on Retinal Expression of Inflammatory Mediators**

To determine whether telmisartan affects inflammatory mediators associated with the pathogenesis of EIU, we analyzed retinal mRNA expression of IL-6, TNF-α, COX-2, iNOS, and MCP-1 at 6 hours after LPS injection by RT-PCR (Fig. 4). Retinal mRNA expressions of these agents in vehicle-treated EIU mice were higher than in normal age-matched control mice. Systemic administration of telmisartan substantially reduced expression of their mRNA.

**Effects of Telmisartan on Anterior Chamber Protein Leakage and Leukocyte Infiltration**

Telmisartan pretreatment led to suppression of leukocyte adhesion to the retinal vasculature in the posterior to anterior (peripheral) region, showing its anti-inflammatory effects on the posterior and intermediate segments of the globe. To evaluate its anti-inflammatory effect on anterior uveitis, we analyzed protein leakage and leukocyte infiltration into the aqueous humor. Protein concentration and leukocyte counts in the aqueous humor of the telmisartan-treated EIU mice were compared with that in vehicle-treated EIU mice (Fig. 5). Telmisartan-treated EIU mice showed a significant (P < 0.01) decrease in the cell counts at 12 and 24 hours after LPS injection compared with vehicle-treated EIU mice (Fig. 5A). Protein concentration in the aqueous humor of the telmisartan-treated EIU mice at 12 and 24 hours after LPS injection tended to be lower than that of vehicle-treated EIU mice, but the difference was not statistically significant (Fig. 5B).
DISCUSSION

The present study demonstrates for the first time that AT1-R upregulation is associated with ocular inflammation in the murine model of EIU and that the AT1-R signaling blockade with telmisartan attenuates several inflammatory parameters including ICAM-1-mediated leukocyte adhesion and infiltration in EIU eyes.

Leukocyte adhesion to the vessel walls is an important process in inflammation. When leukocytes are recruited to inflammatory sites, adhesion molecules play essential roles in the first phase of inflammation. ICAM-1 and its counter receptor β2 (CD18)-integrins (i.e., LFA-1 and Mac-1) regulate the leukocyte-endothelial interaction in the pathogenesis of EIU.\(^8\)–\(^10\) During the development of EIU, ICAM-1 is upregulated and expressed on vascular endothelial cells of the iridociliary body shortly after LPS injection.\(^9\) In addition, several studies have demonstrated that treatment with anti-ICAM-1 antibodies significantly inhibits the development of EIU.\(^5\),\(^10\) In the present study, upregulation of retinal ICAM-1 in EIU was suppressed after pretreatment with telmisartan. This finding is supported by recent data from in vitro assays and in vivo models on systemic hypertension and diabetes, showing that AT1-R blockade attenuates ICAM-1 expression.\(^9\),\(^28\) Recently, we have demonstrated that administration of telmisartan inhibits pathologic, but not physiological, retinal neovascularization in a murine model of ischemic retinopathy, by prevention of
ICAM-1-mediated leukocyte involvement in pathologic neovascularization.29 The present data on EIU as a model of ocular inflammation more strictly confirm the anti-inflammatory effects of AT1-R blockade in the eye.

Besides ICAM-1, various chemical mediators are involved in the pathogenesis of EIU. In the present study, telmisartan treatment led to the suppression of EIU-induced cytokines including IL-6, TNF-α, COX-2, iNOS, and MCP-1. This result is compatible with those reported previously30,31 demonstrating the inhibitory effects of AT1-R blockers on these inflammatory cytokines stimulated by LPS in other organs. The proinflammatory effects of angiotensin II are attributable to its induction of these inflammation-related molecules, most of which are downstream products of nuclear factor (NF)-κB, a transcription factor that promotes the gene expression of various inflammatory cytokines.32 LPS-induced inflammation is mediated by the activation of NF-κB.33 Indeed, ocular inflammation is suppressed by administration of an NF-κB inhibitor in EIU.34 Taken together, the evidence shows that the anti-inflammatory effects of AT1-R blockers most likely result from suppressed gene expression of NF-κB-induced molecules. These previous findings, in accordance with our data, suggest that telmisartan affects not only ICAM-1-mediated leukocyte adhesion but also various inflammatory processes.

In the present study, although anterior-chamber cell infiltration was substantially suppressed by telmisartan, little or no significant change was detected in protein leakage. A similar discrepancy between cell infiltration and protein leakage was also noted in several EIU studies by using neutralizing antibodies against ICAM-1, E-selectin, P-selectin, LFA-1, and IL-10.35 Considering that prostaglandin E2, an inflammatory mediator in addition to the adhesion molecules, is operative in protein leakage and that combined inhibition of both L- and P-selectin suppresses protein leakage,12,34 the cell–protein discrepancy observed in the present and previous studies is most likely attributable to differential mechanisms controlling the multiple inflammatory phases.

Recent reports have revealed that the renin-angiotensin system plays central roles in pathologic vascular conditions including inflammation, angiogenesis, and vascular remodeling.15–20 The renin-angiotensin system has been shown to exist locally in various organs and to promote inflammation-related pathogenesis in atherosclerosis,37 cerebral infarction,38 and pancreatitis.39 AT1-R blockers other than telmisartan are also reported to be anti-inflammatory.37–39 These recent findings suggest the possibility of AT1-R blockade as a therapeutic strategy for these disorders characterized by inflammation. In atherosclerosis, in which angiotensin II promotes the infiltration of monocytes and T lymphocytes, AT1-R blockade with irbesartan suppresses the expression of MCP-1 and subsequent macrophage infiltration.37

**FIGURE 3.** Effects of telmisartan on retinal ICAM-1 expression. RT-PCR (A) Retinal ICAM-1 mRNA expression in EIU mice treated with telmisartan was lower than that in nontreated and vehicle-treated EIU mice. Expression was very low in normal mice. (B) Retinal ICAM-1 protein levels in nontreated or vehicle-treated EIU mice were significantly higher than in normal mice and were significantly suppressed by treatment with telmisartan. The results represent the mean ± SD; n = 6. †P < 0.05 by Mann-Whitney test.

**FIGURE 4.** Effects of telmisartan on retinal expression of inflammatory mediators. Retinal mRNA expression of IL-6, TNF-α, COX-2, iNOS, and MCP-1 in vehicle-treated EIU mice was higher than in normal, age-matched mice and was suppressed by the administration of telmisartan.
which are vulnerable to brain ischemia, AT1-R blockade with candesartan suppresses ICAM-1-dependent leukocyte adhesion to the cerebral vessels, protecting against brain ischemia. In acute pancreatitis, AT1-R blockade with losartan suppresses the production of reactive oxygen species by NADPH oxidase and reduces the severity of inflammation. In addition, an angiotensin-converting enzyme inhibitor, widely used as an anti-hypertensive drug, is also reported to suppress vascular inflammation. In the eye, localization of the renin-angiotensin system has been demonstrated without elucidation of its function, except the possibility of an intraocular pressure modulator. In the present study, AT1-R mRNA and protein expression is shown to be upregulated during the development of EIU. Further, AT1-R blockade suppressed ICAM-1-mediated leukocyte adhesion and infiltration. These results, in accordance with the previous data on inflammation in other organs, suggest the involvement of the renin-angiotensin system in ocular inflammation.

Currently, ocular inflammation such as chronic endogenous uveitis, is treated mainly with topical and/or systemic application of corticosteroids. During the long-term treatment with corticosteroids, however, care must be taken to guard against both ocular and systemic complications, including cataract, glaucoma, diabetes, hypertension, and osteoporosis. Clinically, AT1-R antagonists are widely and safely used in hypertensive patients. Combined with corticosteroid therapy, the anti-inflammatory effects of AT1-R blockade may benefit patients with chronic uveitis to decrease the rate and degree of the corticosteroid-induced complications. The present study is the first to indicate the potential use of AT1-R antagonists as a novel therapeutic strategy to suppress ocular inflammation.

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FIGURE 5. Effects of telmisartan on anterior uveitis. (A) The number of cells in aqueous humor 12 and 24 hours after LPS injection was markedly reduced by treatment with telmisartan. (B) The protein concentration in aqueous humor was not significantly suppressed by the treatment with telmisartan. Vehicle-treated and telmisartan-treated mice. The results represent the mean ± SD; n = 15. *P < 0.01 by Mann-Whitney test.