Olmesartan, a novel AT$_1$ antagonist, suppresses cytotoxic myocardial injury in autoimmune heart failure

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Yuan, Zuyi, Masaoimi Nimata, Taka-aki Okabe, Keisuke Shioji, Koji Hasegawa, Toru Kita, and Chiharu Kishimoto. Olmesartan, a novel AT$_1$ antagonist, suppresses cytotoxic myocardial injury in autoimmune heart failure. Am J Physiol Heart Circ Physiol 289: H1147–H1152, 2005. First published May 6, 2005; doi:10.1152/ajpheart.00078.2005—Some ANG II receptor type 1 (AT$_1$) antagonists are reported to inhibit proinflammatory cytokine production in vitro and in vivo. However, the effects of the drugs on autoimmune diseases are unknown. We tested the hypothesis that olmesartan, a novel AT$_1$ antagonist, ameliorated experimental autoimmune myocarditis (EAM) in rats attributed to the suppression of inflammatory cytokines as well as to the immunomodulatory action of the heart. We administered olmesartan orally at doses of 1, 3, and 10 mg·kg$^{-1}$·day$^{-1}$ to rats with EAM for 3 wk. The results showed that olmesartan decreased blood pressure significantly compared with the untreated group and markedly reduced the severity of myocarditis associated with the decrease of myocardial macrophage, CD4$^+$, and CD8$^+$ T-cell expression by comparison of heart wt-to-body wt ratios, pericardial effusion scores, and macroscopic and microscopic scores. Numbers of myocardial interleukin-1β (IL-1β)-positive-staining cells (obtained by immunohistochemistry) and quantities of IL-1β expression (obtained by Western blotting) were significantly lower in rats with EAM given olmesartan treatment compared with rats given vehicle. Cardiac myosin-specific, delayed-type hypersensitivity was significantly lower in olmesartan-treated rats than in control rats. The cytotoxic activities of lymphocytes in rats with EAM treated with olmesartan were reduced compared with untreated control rats. In vitro study showed that both olmesartan and its active metabolite RNH-6270 suppressed IL-1β production in U-937 cells and cultured myocytes. Olmesartan ameliorates acute EAM in rats. The cardioprotection of olmesartan may be due to suppression of inflammatory cytokines as well as to suppressive effects of cytotoxic myocardial injury in addition to hemodynamic modifications.

angiotensin II type 1; inflammation; cardiomyopathy; myocarditis

IN HUMANS, ACUTE MYOCARDITIS is a potentially lethal disease that frequently precedes the development of dilated cardiomyopathy. Two mechanisms to explain how myocarditis develops into dilated cardiomyopathy have been proposed; one is a persistent viral infection, and the other is progressive autoimmune myocardial injury (8). The autoimmune giant cell myocarditis of rats mimics human fulminant myocarditis in the acute phase (11).

The significance of the renin-angiotensin system in the development of heart failure is now well known (2). ANG II has deleterious effects on heart and kidney. Heart failure patients with high plasma renin levels develop more severe myocardial dysfunction than those with low plasma renin levels. Recent reports indicate that some ANG II type 1 (AT$_1$) receptor antagonists inhibit inflammatory reactions in macrophages (2, 16, 24). AT$_1$ antagonists have also been reported to inhibit interleukin (IL)-1 production (25). These results imply that olmesartan, which is a novel AT$_1$ antagonist, may be an effective agent in countering myocardial inflammation as a result of removal of overproduced cytokines (2, 6, 12, 16, 24, 25). However, the effects of olmesartan on autoimmune heart failure are still unknown.

The purpose of the present study was to examine the effects of olmesartan (15) on an experimental autoimmune myocarditis (EAM) model by focusing on both its inhibitory effects on inflammatory cytokines and on the cytotoxic activities of lymphocytes against myocytes. We chose EAM as an animal model of heart failure in this study.

MATERIALS AND METHODS

Immunization. Acute EAM was induced by immunization with porcine cardiac myosin in 6-wk-old Lewis rats as previously described (19, 20, 27, 28). Porcine cardiac myosin (Sigma) was injected subcutaneously in the foot pads with 0.1 ml of myosin (10 mg/ml) mixed with an equal volume of Freund’s complete adjuvant (FCA) supplemented with Mycobacterium tuberculosis H37Ra (Difco) on days 1 and 8 (19, 20, 27, 28). Control rats were immunized with FCA alone.

Medication. To analyze the hemodynamics of olmesartan on rats without myocarditis, control rats immunized with FCA alone were divided into four groups ($n = 3$ rats/group) for the oral administration of either 0.5% methylcellulose vehicle (Con/V group), 1 mg·kg$^{-1}$·day$^{-1}$ olmesartan (Con/Olm-1 group), 3 mg·kg$^{-1}$·day$^{-1}$ olmesartan (Con/Olm-3 group), or 10 mg·kg$^{-1}$·day$^{-1}$ olmesartan (Con/Olm-10 group) for 3 wk. The olmesartan dosages were determined from reports of previous work (9, 21, 26).

Rats immunized with cardiac myosin (myocarditis rats) were divided into another four groups ($n = 8$ rats/group except vehicle group, where $n = 9$ rats) and were treated with either vehicle (EAM/V group), 1 mg·kg$^{-1}$·day$^{-1}$ olmesartan (EAM/Olm-1 group), 3 mg·kg$^{-1}$·day$^{-1}$ olmesartan (EAM/Olm-3 group), or 10 mg·kg$^{-1}$·day$^{-1}$ olmesartan (EAM/Olm-10 group) for 3 wk. The olmesartan dosages were determined from reports of previous work (9, 21, 26).

All rats were killed on day 22 while under ether anesthesia after hemodynamic measurements (28). The organs were weighed, and the ratio of organ wt-to-body wt was calculated. Olmesartan and its active metabolite RNH-6270 (15) were kindly provided by Sankyo (Tokyo, Japan).

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The protocol was approved by the Institutional Animal Research Committee of Kyoto University.

Histopathology. At death, macroscopic findings were graded on a scale of 0–4, and pericardial effusion was graded as 0–2 as previously described (19, 20, 27, 28). Microscopic findings for myocardial damage and cellular infiltration were graded on a scale of 0–4 as previously described (19, 20, 27, 28). After macroscopic examination, a part of the ventricles was embedded in optimum cutting temperature compound for immunohistochemistry; remnant tissues were kept at −80°C for Western blotting.

Immunohistochemical assay. We used an immunoperoxidase technique to perform immunohistochemistry for anti-IL-1β and cell surface markers as previously described (19, 20, 27, 28). The following primary antibodies were used: anti-IL-1β (Serotec); ED1 (for macrophages; Serotec), W3/25 (for CD4 cells; Serotec); and OX8 (for CD8 cells; Serotec). The numbers of positive-staining cells within the heart tissue were counted by two blinded observers in six fields at ×400 magnification (within a 1-mm² grid), and the total number of positive-staining cells for the six fields was recorded as the number of infiltrating cells in the lesions.

Western blotting. The myocardial lysates were electrophoresed using SDS-PAGE and were sequentially electrophoretically transferred to a membrane (Millipore). The membrane was incubated with an anti-IL-1β (Serotec) antibody and then with a peroxidase-linked secondary antibody (Amersham). Chemiluminescence was detected and semiquantitatively analyzed using the NIH Image system as previously described (19, 27, 28).

Delayed-type hypersensitivity. Myosin-specific delayed-type hypersensitivity (DTH) was quantified on day 20 using a standard hindlimb footpad swelling assay. Maximal swelling was found at 48 h after injection.

Cell culture. To culture splenocytes and lymph node (LN) cells, spleens and LNs were harvested from Lewis rats at death, and single-cell suspensions were obtained by passing cells through a stainless steel mesh screen. Cells were suspended in RPMI-1640 supplemented with fetal calf serum (FCS), 1% sodium pyruvate, 1% nonessential amino acids, 5 × 10⁻³ M 2-mercaptoethanol, and a penicillin-streptomycin mixture.

To culture neonatal rat cardiomyocytes, cardiac ventricles from 1- to 4-day-old Lewis rats were minced and dissociated with 0.125% trypsin. Cardiomyocytes (2 × 10⁴ cells/well) were incubated in 96-well plates in 10% FCS-supplemented Dulbecco’s modified essential medium (DMEM) at 37°C. Bromodeoxyuridine (100 μmol/l) was added during the first 48 h to prevent the proliferation of nonmyocyte cells.

Cytotoxicity assays. Lewis rats were immunized with cardiac myosin, treated with various dosages of olmesartan or vehicle, and killed on day 22. LN cells from rats treated with olmesartan or vehicle were used as effector cells. F-2 cells (murine endothelial cells) and cardiomyocytes plated in 96-microwell plates (2 × 10⁴ cells/well) were labeled with sodium chromate at 1 μCi/well (²⁵Cr; Amersham International) for 1 h. After labeled target cells had been washed with phosphate-buffered saline (PBS) three times, LN cells were incubated at effector/target ratios of 100:1 and 200:1 for 4 h. The supernatant was collected, and the radioactivity of ²⁵Cr released into the supernatant was measured using a gamma counter. The percentage of cytotoxicity was calculated using the formula:

\[
\text{percent cytotoxicity} = \left( \frac{E - S}{M - S} \right) \times 100
\]

where \(E\) is the number of counts per minute (cpm) released in the presence of effector cells, \(S\) is the number of spontaneous counts per minute released from target cells incubated in the medium, and \(M\) is the maximal number of counts per minute released from target cells incubated with 2% Triton X-100.

Cytokine assays. U-937 human macrophage cells and cultured rat myocytes were stimulated with 10 μg/ml lipopolysaccharide (LPS). Olmesartan or its active metabolite RNH-6270 (15) was added to the medium 30 min before LPS stimulation. Forty-eight hours later, IL-1β in the medium was assayed by ELISA using commercially available kits (R&D Systems).

Statistics. All values are expressed as means ± SD. One-way ANOVA and subsequent Fisher protected least-significant difference tests were performed. A value of \(P < 0.05\) was considered statistically significant.

RESULTS

Hemodynamics of olmesartan treatment in rats with and without EAM. In control rats, middle and high doses of olmesartan (3 and 10 mg·kg⁻¹·day⁻¹, respectively) decreased blood pressure significantly and tended to increase HR compared with the vehicle group (Table 1). However, there were no significant differences in blood pressure or HR in the groups treated with a low dose (1 mg·kg⁻¹·day⁻¹) of olmesartan compared with the vehicle group.

In rats with EAM, none died during the course of the disease. Blood pressure was decreased in olmesartan-treated groups (Table 1). There were no significant differences in HR among the four groups.

Histopathology and heart wt-to-body wt ratios in rats with acute EAM. On day 22 at death, hearts showed severe and diffuse discolored myocarditis with massive pericardial effusion in rats immunized with cardiac myosin. Extensive injuries to myocytes with inflammatory changes and multinucleated giant cells (Fig. 1B, arrows) were observed. Treatment with 1, 3, and 10 mg·kg⁻¹·day⁻¹ olmesartan reduced the severity of the disease as assessed by measuring heart wt-to-body wt and organ wt-to-body wt ratios, pericardial effusion, and macroscopic and microscopic scores (Table 2 and Fig. 1). The percentages of macrophages and CD4⁺ and CD8⁺ T cells recruited into the lesions were significantly reduced by the 1 mg·kg⁻¹·day⁻¹ olmesartan treatment (Table 2).

Myocardial IL-1β expression. Immunohistochemistry showed that IL-1β-positive cells were localized mainly in infiltrating inflammatory cells (Fig. 2, A and C, arrows). Olmesartan treatment markedly reduced the number of IL-1β-positive cells in the inflammatory lesions compared with rats with EAM and vehicle treatment (Fig. 2, B and D). Western blotting showed that myocardial IL-1β was upregulated 2.4-fold in rats with EAM and vehicle treatment compared with intact heart (Fig. 2).

Table 1. Hemodynamics of olmesartan on rats with and without EAM

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart Rate, beats/min</th>
<th>Systolic Blood Pressure, mmHg</th>
<th>Diastolic Blood Pressure, mmHg</th>
<th>Heart Wt/Body Wt Ratio, mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>447±55</td>
<td>127±4</td>
<td>95±4</td>
<td>3.25±0.36</td>
</tr>
<tr>
<td>Olm-1</td>
<td>407±39</td>
<td>110±9</td>
<td>86±7</td>
<td>3.18±0.28</td>
</tr>
<tr>
<td>Olm-3</td>
<td>455±28</td>
<td>108±7*</td>
<td>78±12*</td>
<td>3.32±0.19</td>
</tr>
<tr>
<td>Olm-10</td>
<td>466±26</td>
<td>104±8*</td>
<td>77±9†</td>
<td>3.30±0.20</td>
</tr>
<tr>
<td>Rats with EAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>443±55</td>
<td>120±10</td>
<td>89±11</td>
<td>4.56±0.21</td>
</tr>
<tr>
<td>Olm-1</td>
<td>446±22</td>
<td>109±13*</td>
<td>81±8†</td>
<td>3.82±0.31*</td>
</tr>
<tr>
<td>Olm-3</td>
<td>445±30</td>
<td>94±8*</td>
<td>67±11*</td>
<td>4.02±0.46†</td>
</tr>
<tr>
<td>Olm-10</td>
<td>468±62</td>
<td>96±8*</td>
<td>68±15*</td>
<td>4.05±0.48†</td>
</tr>
</tbody>
</table>

Values are means ± SD; \(n\), no. of rats/group. Normal rats and rats with experimental autoimmune myocarditis (EAM) were treated with vehicle or Olm-1, Olm-3, or Olm-10 (1, 3, or 10 mg·kg⁻¹·day⁻¹ olmesartan, respectively). *P < 0.01; †P < 0.05 vs. vehicle or myocarditis groups.
Olmesartan treatment decreased the upregulated IL-1β expression in EAM (Table 3). The findings of myocardial IL-1β expression in relation to the severity of lesions were constant.

**Myosin DTH.** We investigated whether the antiinflammatory property of olmesartan suppressed the immune response by assaying DTH to cardiac myosin. As a result, myosin DTH was significantly lower in olmesartan-treated (1 mg·kg⁻¹·day⁻¹) rats with myocarditis than in untreated rats with myocarditis (Table 3). Reduced DTH reaction was not seen in myocarditis rats treated with 3 and 10 mg·kg⁻¹·day⁻¹ olmesartan.

**Cytotoxic activity of lymphocytes.** The cytotoxic activities of lymphocytes against F-2 cells and cardiomyocytes were examined. At effector/target ratios of 100:1 and 200:1, the cytotoxic activities of lymphocytes from rats immunized with cardiac myosin treated with 1 but not 3 or 10 mg·kg⁻¹·day⁻¹ olmesartan were significantly suppressed compared with those from rats immunized with cardiac myosin and treated with PBS.

**Effects of drugs on IL-1β production in vitro.** IL-1β production was markedly increased by LPS stimulation (Table 4). Both olmesartan and RNH-6270 suppressed LPS-induced increased IL-1β production on U-937 cells and rat myocytes in a dose-dependent manner (Table 4).

**DISCUSSION**

The present findings clearly demonstrate that olmesartan, which is a novel AT₁ antagonist, reduced the severity of acute myocarditis.

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**Table 2. Pathology of olmesartan in rats with EAM**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Heart Wt/Body Wt Ratio, mg/g</th>
<th>Lung Wt/Body Wt Ratio, mg/g</th>
<th>Liver Wt/Body Wt Ratio, mg/g</th>
<th>Kidney Wt/Body Wt Ratio, mg/g</th>
<th>Pericardial Effusion Score</th>
<th>Macroscopic Score</th>
<th>Microscopic Score</th>
<th>Myocardial Lymphocyte Subset, %</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Macrophage</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>9</td>
<td>4.56±0.21</td>
<td>6.75±0.96</td>
<td>48.2±4.1</td>
<td>9.24±0.39</td>
<td>1.5±0.6</td>
<td>2.7±0.9</td>
<td>2.8±1.4</td>
<td>20.0±1.9</td>
</tr>
<tr>
<td>Olm-1</td>
<td>8</td>
<td>3.82±0.31*</td>
<td>5.55±0.34*</td>
<td>39.4±3.9*</td>
<td>9.39±0.51</td>
<td>0.8±0.3†</td>
<td>1.8±1.0†</td>
<td>1.1±0.4*</td>
<td>13.7±1.9</td>
</tr>
<tr>
<td>Olm-3</td>
<td>8</td>
<td>4.02±0.46†</td>
<td>5.61±0.57*</td>
<td>39.5±3.1*</td>
<td>9.79±0.95</td>
<td>1.2±0.7</td>
<td>2.5±0.9</td>
<td>1.8±1.0†</td>
<td>16.8±2.4</td>
</tr>
<tr>
<td>Olm-10</td>
<td>8</td>
<td>4.05±0.48†</td>
<td>5.64±0.59*</td>
<td>41.8±6.4†</td>
<td>9.78±0.70</td>
<td>1.4±0.5</td>
<td>2.2±0.9</td>
<td>2.0±0.8†</td>
<td>17.8±2.2</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of rats. For myocardial lymphocyte subset, the positive-staining cells of heart tissue were calculated. *P < 0.01; †P < 0.05 vs. myocarditis.
Table 3. Myocardial IL-1β expression, myosin DTH, and cytotoxic activities of olmesartan

<table>
<thead>
<tr>
<th>Group</th>
<th>IL-1β Expression, %</th>
<th>Myosin DTH, mm × 10⁻²</th>
<th>Cytotoxic Activity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Against F-2 Cells</td>
</tr>
<tr>
<td>Normal</td>
<td>1.0</td>
<td>15.9 ± 4.1</td>
<td>16.0 ± 3.0</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>3.1 ± 0.6</td>
<td>35.5 ± 2.6</td>
<td>22.1 ± 4.1</td>
</tr>
<tr>
<td>Olm-1</td>
<td>1.4 ± 0.7</td>
<td>20.3 ± 4.1</td>
<td>11.3 ± 3.4</td>
</tr>
<tr>
<td>Olm-3</td>
<td>1.7 ± 0.5</td>
<td>30.5 ± 3.5</td>
<td>11.8 ± 3.4</td>
</tr>
<tr>
<td>Olm-10</td>
<td>1.8 ± 0.4</td>
<td>31.1 ± 4.4</td>
<td>18.2 ± 3.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. *Densitometric analysis of relative protein levels is shown. Values were derived from four animals and are represented as percentage of controls. **Myosin delayed-type hypersensitivity (DTH) expressed as footpad response. Values are derived from five animals and are categorized by effector/target ratio. d,e,f,n. no. of rats = 5, 9, or 8, respectively. •P < 0.01 vs. normal; gP < 0.01; hP < 0.05 vs. myocarditis.
chotted to evaluate the effects of olmesartan and RNH-6270 on the production of cytokines and transcription of cytokine genes in vitro and in vivo. In the present study, cytokine production and transcription of cytokine genes in EAM in rats with EAM, and that the cardioprotection of olmesartan may be due to the suppression of both inflammatory cytokines and cytotoxic activity of lymphocytes against heart in addition to hemodynamic modifications.

Several clinical studies have described the participation of proinflammatory cytokines in the pathogenesis of cardiac diseases. The levels of circulating proinflammatory cytokines such as tumor necrosis factor (TNF-α) and IL-1 and -6 are elevated in patients with myocarditis. In a murine model of viral myocarditis, the intracardiac expression of TNF-α, IL-1β, interferon-γ, and IL-2 genes was increased. The degree of expression was correlated with the severity of the disease, which suggests that the overproduction of proinflammatory cytokines may aggravate the disease. This is supported in part by recent reports that the overexpression of TNF-α in heart caused severe myocarditis and cardiomyopathy in transgenic mice (13), and IL-1β as well as TNF-α promote the aggravation of viral myocarditis in virus-resistant mice (10, 14). It was therefore demonstrated that the suppression of inflammatory cytokines has beneficial effects in ameliorating acute myocarditis. Accordingly, we focused on myocardial IL-1β expression as a significant marker to reflect the effects of olmesartan.

AT1 antagonists such as olmesartan are reported to suppress cytokine production and transcription of cytokine genes in vitro and in vivo (2, 6, 12, 16, 24, 25). In the present study, olmesartan treatment modified the increased IL-1β expression in acute EAM, and the immunohistochemical study showed that the numbers of macrophages, CD4+ and CD8+ T cells, and IL-1β-positive inflammatory cells were markedly reduced by olmesartan treatment. In addition, both olmesartan and its active metabolite RNH-6270 suppressed IL-1β production in vitro. Accordingly, it may be that the beneficial effects of olmesartan in EAM may be partly due to suppression of inflammatory events in the myocardium. The molecular mechanisms of olmesartan in the suppression of inflammatory cytokines are not fully understood. However, inhibition of signal transduction pathways such as nuclear factor-kB (which is particularly important in the expression of cytokines) by AT1 antagonists has been postulated (2, 6, 12, 16, 24, 25).

Another important role of olmesartan is immunomodulation. Potential immunoregulatory effects of ANG II such as T-cell chemotaxis have been reported (5, 25). Accordingly, olmesartan, a novel AT1 antagonist, may exhibit immunosuppressive properties. Although it is unknown whether olmesartan directly affects the host immune status, it was demonstrated in this study that the DTH reaction of rats immunized with myosin treated with low-dose olmesartan (1 mg·kg⁻¹·day⁻¹) was suppressed compared with rats immunized with myosin and treated with PBS. This suggests that olmesartan treatment reduced antigen-specific DTH activity in the host. Accordingly, the overall effects of olmesartan could induce the suppression of autoimmune myocarditis associated with the reduction of cytotoxic activity against myocytes; i.e., olmesartan suppressed cytotoxic myocardial injury in autoimmune heart failure in rats. Indeed, the cytotoxic activities of lymphocytes against F-2 cells and cultured myocytes in rats with EAM treated with low-dose olmesartan were reduced compared with untreated controls.

The reason that middle or high doses of olmesartan were not as effective for cardioprotection is unknown. However, as shown in Table 1, there was a relative hypotensive tendency in rats treated with middle- and high-dose but not low-dose olmesartan. That is, there might be a possibility that coronary perfusion pressure may fall to <90 mmHg in mice treated with middle- or high-dose olmesartan to result in small improvement of cardiac pathology. A similar therapeutic dilemma between hemodynamic and nonhemodynamic effects was also noted for benedipine, a calcium channel antagonist (27). Accordingly, a primary factor for this drug might be at least partly related to the propensity or capacity of hemodynamic modifications. Although the actual effects might be different between drugs, dosages, and experimental models, lower or minimally hemodynamic doses appear warranted.
failure by reducing cytokines and oxidative stress and by demonstrating antiinflammation (7, 9, 21, 26). At the present time, the capacity to suppress cytotoxic activities of lymphocytes might be unique for olmesartan.

In conclusion, olmesartan, a recently developed AT₁ antagonist, ameliorates acute EAM in rats. The cardioprotection of olmesartan may be due to the suppression of inflammatory cytokines as well as immunosuppressive effects for cytotoxic myocardial injury in addition to hemodynamic modifications.

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