Effects of atorvastatin on vascular remodeling in spontaneously hypertensive rats

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Abstract: Objective: To investigate the structural changes of aorta, and evaluate the effects of atorvastatin on the remodeling of thoracic aorta in spontaneously hypertensive rats (SHR). Methods: Twelve eight-week-old SHR were randomized into atorvastatin treated group (ATV group, n = 6) and distilled water group (DW group, n = 6); Wistar-Kyoto rats (WKY) were used as normal controls. Atorvastatin was administered to ATV group for 10 weeks by gavage in mixture with distilled water (1 ml); the latter two groups were given the same amount of distilled water by gavage for 10 weeks. Systolic blood pressure of caudal artery was examined before and after treatment, and serum concentrations of total cholesterol, triglycerides and HDL-C were measured. Wall thickness, media thickness, medial cross-sectional area and lumen diameter of thoracic aorta were assessed with computed video processing. Results: Systolic blood pressure in ATV group was markedly lower than that in DW group (P < 0.01). Compared with DW group and WKY group, serum concentrations of total cholesterol, triglycerides and HDL-C in ATV group were significantly lower (P < 0.01, P < 0.05). Wall thickness, media thickness, and medial cross-sectional area to lumen ratio in DW group were significantly higher than those in WKY group and ATV group (P < 0.01, P < 0.05), but no such difference was found between WKY group and ATV group (P > 0.05). Conclusion: Vascular structural changes of aorta are due to the alteration of the vessel wall in early stage of SHR. Atorvastatin can markedly improve vascular remodeling.

Key words: Atorvastatin, Hypertension, Vascular remodeling

INTRODUCTION

Hypertension is always accompanied by increases in artery wall thickness, mainly caused by proliferation, hypertrophy, migration and apoptosis of vascular smooth muscle cells (VSMC), and elevated content of connective tissue. These structural changes in blood vessels are known as vascular remodeling (Dzau et al., 1994). Recent study showed that statins such as atorvastatin had pleiotropic effects: inhibiting VSMC proliferation and migration, facilitating VSMC apoptosis, and ameliorating endothelial function (Belosta et al., 2000). Past researches in this field mainly focused on small arteries, less on big ones. Moreover, there are still several unsolved problems: during the development of hypertension, what are the characters of thoracic aorta remodeling? And what are the effects of atorvastatin on aortic remodeling? With the model of spontaneously hypertensive rats, we investigated the structural changes of aorta, and evaluated the effects of atorvastatin on aortic remodeling.

MATERIALS AND METHODS

Drugs and chemicals

Atorvastatin was donated by Pfizer Pharmaceuticals, Ltd. (Dalian, China). Lipids test kits: cholesterol, triglycerides and HDL were products of No.1 Chemical Company, Japan.

Rats and treatment

Eighteen eight-week-old spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY) (SHR 12, WKY 6, Grade II), male, body weight 118g ± 3g respectively, were purchased from the Department of Pharmacology, the Second Military University. After measurement of systolic blood pressure (SBP), SHR
were randomized into atorvastatin treated group (ATV group, n = 6) and distilled water group (DW group, n = 6), with WKY as normal controls. Atorvastatin mixed with 1 ml distilled water was administered to ATV group for 10 weeks by gavage. While, the latter two groups were given 1 ml distilled water by gavage.

Systolic blood pressure (SBP) measurement and materials taken from the rats

SBP was measured in conscious rats using tail-cuff technique (HX-II computer control sphygmomanometer for rats, Laboratory of Cardiovascular Physiology, Hunan Medical University) before and at the end of the treatment. At the end of the ten-week treatment, the rats were anesthetized by 2% soluble pentobarbitone; 2 ml arterial blood was drawn for determination of serum concentrations of total cholesterol, triglycerides and HDL-C. The thoracic aorta was removed and treated carefully by Hanks’ balance solutions, then immersed in 10% formaldehyde. After desiccation, and being hyaline and paraffin embedded, was cut into 4μm sections for hematoxylin and eosin (HE) staining.

Lipids measurement

Arterial blood (2 ml) was centrifuged (2000 r/min x 5 min) to have the serum isolated. Total cholesterol (TC), triglycerides (TG) and HDL-C were measured in a routine diagnostic analyzer (Hitachi, 7600) using enzymatic colorimetric assays (TC, CHOD-PAP assay; TG, GPO-PAP assay; and HDLs, PEG-cholesterol esterase-cholesterol oxidase assay).

Morphometric analysis of vascular wall thickening

Four points in every vascular circle was perpendicularly chosen as measurement areas in the sections stained with HE. Wall thickness, media thickness, medial cross-sectional area and lumen diameter of thoracic aorta were assessed with computed video processing (Institute of Biochemical Engineering and Apparatus Science, Zhejiang University).

Statistical analysis

Data were expressed as x ± s; comparison between two groups was done by t test and analysis of variance. All above were processed by software SPSS 10.0. P < 0.05 indicated statistical significance.

RESULTS

Effect of atorvastatin on SBP

SBP in ATV group and DW group were equal before the treatment began, and were higher than that in WKY group (P < 0.01). After the ten-week treatment, SBP in ATV group was markedly decreased (P < 0.01) compared with that before treatment or in DW group, while SBP in WKY group stayed at a nearly stable level (Table 1).

<table>
<thead>
<tr>
<th>Groups</th>
<th>8 weeks</th>
<th>18 weeks</th>
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<tbody>
<tr>
<td>WKY</td>
<td>108.33 ± 4.18</td>
<td>119.67 ± 1.63</td>
</tr>
<tr>
<td>DW</td>
<td>153.83 ± 4.40</td>
<td>173.33 ± 3.78</td>
</tr>
<tr>
<td>ATV</td>
<td>155.69 ± 4.96</td>
<td>134.17 ± 3.60</td>
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n = 6 rats. * P < 0.01, VS DW group; † P < 0.01, VS WKY group

Comparison of TC, TG and HDL-C in three groups

After the ten-week treatment, serum concentrations of TC, TG and HDL-C in ATV group were significantly lower compared with DW group and WKY group (P < 0.01, P < 0.05) (Table 2).

<table>
<thead>
<tr>
<th>Groups</th>
<th>TC (mmol/L)</th>
<th>TG (mmol/L)</th>
<th>HDL-C (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>1.49 ± 0.38</td>
<td>1.09 ± 1.46</td>
<td>0.82 ± 0.23</td>
</tr>
<tr>
<td>DW</td>
<td>1.53 ± 0.22</td>
<td>1.18 ± 1.55</td>
<td>0.79 ± 0.13</td>
</tr>
<tr>
<td>ATV</td>
<td>1.03 ± 0.16</td>
<td>0.71 ± 0.19</td>
<td>0.62 ± 0.14</td>
</tr>
</tbody>
</table>

n = 6 rats. * P < 0.05; † P < 0.01, VS ATV group

Morphometric parameters of the thoracic aorta remodeling in every group

Wall thickness, media thickness, and medial cross-sectional area, to lumen ratio in various groups, the parameters in DW group were significantly higher than those in WKY group and ATV group (P < 0.01, P < 0.05), but no such difference was found between WKY group and