Antiinflammatory and Antiarteriosclerotic Actions of HMG-CoA Reductase Inhibitors in a Rat Model of Chronic Inhibition of Nitric Oxide Synthesis

Weihua Ni, Kensuke Egashira, Chu Kataoka, Shiro Kitamoto, Masamichi Koyanagi, Shujiro Inoue, Akira Takeshita

Abstract—Recent studies suggest that some of the beneficial effects of 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) may be due to their cholesterol-lowering independent effects on the blood vessels. Chronic inhibition of endothelial nitric oxide (NO) synthesis by oral administration of \( N^\text{G} - \text{nitro-L-arginine methyl ester (L-NAME)} \) to rats induces early vascular inflammation as well as subsequent arteriosclerosis. The aim of the study is to test whether treatment with statins attenuates such arteriosclerotic changes through their cholesterol-lowering independent effects. We investigated the effect of statins (pravastatin and cerivastatin) on the arteriosclerotic changes in the rat model. We found that treatment with statins did not affect serum lipid levels but markedly inhibited the L-NAME--induced vascular inflammation and arteriosclerosis. Treatment with statins augmented endothelial NO synthase activity in L-NAME--treated rats. We also found the L-NAME induced increase in Rho membrane translocation in hearts and its prevention by statins. Such vasculoprotective effects of statins were suppressed by the higher dose of L-NAME. In summary, in this study, we found that statins such as pravastatin and cerivastatin inhibited vascular inflammation and arteriosclerosis through their lipid-lowering independent actions in this model. Such antiarteriosclerotic effects may involve the increase in endothelial NO synthase activity and the inhibition of Rho activity. (Circ Res. 2001;89:415-421.)

Key Words: arteriosclerosis ■ endothelium-derived factors ■ inflammation ■ monocyte chemoattractant protein-1 ■ nitric oxide synthase

Recent studies suggest that 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) reduce the incidence of myocardial infarctions and ischemic strokes.\(^1\,\,^2\) The beneficial effects of statins are likely to result from stabilization of unstable atheroma prone to rupture, because cholesterol-lowering therapy with statins increases markers of plaque stability.\(^3\,\,^4\) Although such effects of statins are predominantly attributed to their lipid-lowering effects, subgroup analysis of the data from clinical trials suggests that there may be beneficial effects independent of their cholesterol-lowering effects.\(^1\,\,^2\,\,^5\) Endothelium-dependent nitric oxide (NO)-mediated vasodilatation has been demonstrated to improve at the early phase of statin treatment in humans.\(^6\,\,^7\,\,^8\) It is recently reported that addition of statins to cultured human endothelial cells increases endothelial-type NO synthase expression and activity.\(^9\) Thus, one may hypothesize that some of the beneficial effects of statins may be due to their cholesterol-lowering independent effects on endothelial cells. However, it is unclear whether statins attenuate cardiovascular inflammation and arteriosclerosis in vivo through their cholesterol-lowering independent effects.

Endothelium-derived NO has been recognized to be an antiinflammatory and antiarteriosclerotic molecule. Mice lacking endothelial-type NO synthase exhibit hypertension and an enhanced vascular remodeling in response to injury.\(^10\) We recently reported that chronic inhibition of NO synthesis by administration of \( N^\text{G} - \text{nitro-L-arginine methyl ester (L-NAME)} \) induces early inflammation (monocyte infiltration into the coronary vessels associated with induction of monocyte chemoattractant protein-1 [MCP-1] expression) and subsequent arteriosclerosis (medial thickening and perivascular fibrosis) in the rats.\(^11\,\,^12\) The importance of our observation is supported by the well-recognized concept that the adhesion of mononuclear cells to, and their infiltration into, the blood vessel wall have been assumed to be crucial early events of arteriosclerosis.\(^13\)

Such rat model may be useful to investigate lipid-lowering independent antiarteriosclerotic effects of statins, because administration of statins even at high doses to normal rats does not change serum cholesterol levels.\(^14\) Accordingly, in the present study, we used this rat model to investigate the antiarteriosclerotic actions of statins.

Original received May 9, 2001; revision received July 25, 2001; accepted July 25, 2001.

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TABLE 1. Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 0</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>134±4</td>
<td>132±3</td>
<td>130±6</td>
<td>133±6</td>
<td>128±4</td>
<td>138±8</td>
</tr>
<tr>
<td>L</td>
<td>138±5</td>
<td>167±3*</td>
<td>186±6*</td>
<td>191±9*</td>
<td>188±5*</td>
<td>180±4*</td>
</tr>
<tr>
<td>L⊂P50</td>
<td>141±3</td>
<td>170±7*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>L⊂P100</td>
<td>128±4</td>
<td>163±12*</td>
<td>135±8</td>
<td>140±8</td>
<td>145±7</td>
<td>143±9</td>
</tr>
<tr>
<td>L⊂P250</td>
<td>131±4</td>
<td>169±7*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>L⊂C1</td>
<td>142±5</td>
<td>167±12*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>L⊂C2</td>
<td>136±3</td>
<td>163±5*</td>
<td>149±5</td>
<td>151±7</td>
<td>155±9</td>
<td>140±5</td>
</tr>
<tr>
<td>L⊂C10</td>
<td>127±5</td>
<td>171±7*</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Values are expressed as mm Hg.

*P<0.05 vs control group; †P<0.05 vs day 0. ND indicates not determined.

Materials and Methods

Animals and Experimental Protocol

The present study protocol was reviewed and approved by the Committee on Ethics on Animal Experiments, Kyushu University Faculty of Medicine, and the experiments were conducted according to the Guidelines for Animal Experiments of Kyushu University Faculty of Medicine. Twenty-week-old male Wistar-Kyoto rats were obtained from an established colony at the Animal Research Institute of Kyushu University Faculty of Medicine.

Several groups of 20-week-old male Wistar-Kyoto rats were studied. The control group received untreated chow and drinking water. L group received L-NNAME in drinking water (1 mg/mL). Lx+Py group received L-NNAME in drinking water (1.0 or 1.8 mg/mL) and pravastatin sodium (50, 100, or 250 mg/kg per day, dissolved in 5% carboxymethyl cellulose sodium solution and given by gavage). Lx+Cy group received L-NNAME in drinking water and cerivastatin sodium intraperitoneally (1, 2, or 10 mg/kg per day). Treatment with statins was started 2 days before L-NNAME administration was begun. On day 3 of L-NNAME administration, systolic blood pressure (the tail-cuff method) was measured. Then the rats were anesthetized and euthanized for morphometric, immunohistochemical, and biological analyses. Furthermore, some rats in the control, L-NNAME, L1.0+P100, and L1.0+C2 groups were euthanized on day 28 for morphometric analysis. Pravastatin sodium and cerivastatin sodium were generously provided by Sankyo Co, Ltd (Tokyo) and Bayer Yakuhin, Ltd (Osaka), respectively.

Biochemical Analysis

Serum total cholesterol, triacylglycerol, and HDL cholesterol levels were determined with commercially available kits from Wako Pure Chemicals. Serum levels of L-NNAME and N^o-nitro-L-arginine (L-

Histopathology and Immunohistochemistry

Histopathology and Immunohistochemistry were performed as described.11 Some sections were subjected to immunostaining using antibodies against rat macrophage/monocytes (ED-1, Serotec, Oxford, UK), proliferating cell nuclear antigen (PCNA) (Dako A/S, Glostrup, Denmark), endothelial NO synthase (eNOS) and inducible NO synthase (iNOS) (Transduction Laboratories), or nonimmune IgG (Zymed Laboratory Inc). Cell enumeration was performed as described.11,12 Evaluation of the medial thickness and perivascular fibrosis of coronary arteries on day 28 was performed as previously described.11

Western Blot Analysis

Proteins were prepared from the aorta and heart and separated on SDS-PAGE as described.20 Immunoblotting was performed using

TABLE 2. Serum Lipid Levels, L-NNA Concentration, and Tissue ACE Activity

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Cholesterol, mmol/L Day 3</th>
<th>HDL Cholesterol, mmol/L Day 3</th>
<th>TG, mmol/L Day 3</th>
<th>L-NNA, μmol/L Day 3</th>
<th>Cardiac ACE Activity, nmol/mg per hr Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.2±0.2 (1.1±0.3)</td>
<td>1.1±0.03 (1.0±0.05)</td>
<td>0.29±0.06</td>
<td>ND</td>
<td>0.72±0.02</td>
</tr>
<tr>
<td>L</td>
<td>2.9±0.2 (1.1±0.02)</td>
<td>1.13±0.04 (1.1±0.02)</td>
<td>0.39±0.05</td>
<td>ND</td>
<td>1.19±0.19*</td>
</tr>
<tr>
<td>L⊂P50</td>
<td>2.7±0.1 (0.99±0.05)</td>
<td>ND</td>
<td>0.38±0.05</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>L⊂P100</td>
<td>3.1±0.2 (1.07±0.12)</td>
<td>1.2±0.01 (1.2±0.01)</td>
<td>0.38±0.06</td>
<td>ND</td>
<td>1.27±0.1*</td>
</tr>
<tr>
<td>L⊂P250</td>
<td>2.8±0.1 (1.01±0.04)</td>
<td>ND</td>
<td>0.36±0.03</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>L⊂C1</td>
<td>2.6±0.2 (1.06±0.08)</td>
<td>ND</td>
<td>0.37±0.05</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>L⊂C2</td>
<td>2.7±0.1 (0.96±0.04)</td>
<td>1.1±0.01 (1.1±0.01)</td>
<td>0.39±0.04</td>
<td>0.38±0.03</td>
<td>1.17±17*</td>
</tr>
<tr>
<td>L⊂C10</td>
<td>3.3±0.2 (1.07±0.12)</td>
<td>ND</td>
<td>0.43±0.05</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Data are mean±SE. n=7 to 8. ND indicates not determined; (−), below the detection level (<0.02 μmol/L).

*P<0.05 vs control group.
monoclonal antibodies to eNOS, iNOS (Transduction Laboratories), and to RhoA (Santa Cruz Biotechnology Inc). Immunodetection was accomplished using appropriate horseradish peroxidase–linked secondary antibody and the enhanced chemiluminescence (ECL) kit (Amersham Corp). Membrane and cytosolic proteins in cardiac tissue were isolated as described previously. Immunoblotting for RhoA in membrane and cytosolic fraction was performed as described above.

**Statistical Analysis**

Data are expressed as mean ± SE. Statistical analysis of differences was compared by ANOVA and Bonferroni’s multiple comparison test. A level of $P<0.05$ was considered statistically significant.

**Results**

**Systolic Arterial Pressure and Serum Lipids and L-NA**

The L group showed a progressive rise in systolic arterial pressure throughout the study (Table 1). This increase in systolic blood pressure showed no significant change in all groups with statin treatment on day 3, whereas it was normalized on days 7, 14, 21, and 28 of treatment in the L.0+P100 and L.0+C2 groups.

Serum total, HDL cholesterol, and triacylglycerol concentrations in the statin-treated rats were not statistically different from those seen in control or L-NAME–treated rats (Table 2). Serum L-NAME and L-NNA concentrations were measured on day 3 of L-NAME treatment. L-NNA was not detected in the serum of control rats. In the L group, L-NNA concentration was $111.0 ± 15$ mmol/L, which was not significantly different from those in the L.0+P100 or L.0+C2 groups (Table 2). Serum L-NAME was below detection level (<0.02 µmol/L) in all groups (data not shown), indicating conversion of L-NAME to L-NNA after absorption.21

**Effect of Statins on Local ACE Activity**

Cardiac ACE activity was increased in the L group on day 3. This increased ACE activity was not influenced by treatment with statins (Table 2).

**Effects of Statins on Inflammatory and Proliferative Changes**

We found no evidence of inflammation in the control rats (Figure 1A). In contrast, on day 3, attachment of mononuclear leukocytes to the endothelium of coronary vessels and their infiltration into the vessel wall were noted in the L group (Figure 1A). A marked mononuclear leukocyte infiltration into the perivascular area and the myocardial interstitial area was also observed in this group. The majority of these cells were found to be ED-1–positive monocytes (Figure 1A). Nuclear staining with PCNA antibody was observed in some endothelial cells, vascular smooth muscle cells in the media, monocytes, and myofibroblast-like cells (Figure 1A).

When ED-1–positive monocytes or PCNA-positive cells were counted by a single observer who was blind to the treatment protocols, the number of immunopositive cells per section was significantly greater in the L group than in the control group (Figure 2). The increases in ED-1–positive cells and PCNA positive cells were significantly reduced by treatment with statins in a dose-dependent manner (Figures 2A through 2D).

**Effects of Statins on MCP-1 and TGF-β1 Gene Expression**

When cardiac MCP-1 and TGF-β1 mRNA levels were examined by Northern blot analysis in the control, L-NAME, L.0+P100, and L.0+C2 groups on day 3, both MCP-1 and TGF-β1 mRNA levels were significantly increased in L group. Such increased gene expressions were significantly reduced in the L.0+P100 and L.0+C2 groups (Figure 3).

**Effect of Statins on NO Synthase Expression and Activity**

NOx-generating capacity from the aortic segments was examined in the control, L, L.0+P100, and L.0+C2 group. NOx-generating capacity in the thoracic aorta was markedly decreased in the L group. The blunted NOx-generating capacity by L-NAME was significantly restored by statin treatment (Figure 4A). To provide a direct evidence suggesting restoration of NO production in vivo, serum NOx was measured by a fluorometric assay. Serum NOx concentration...
was significantly decreased in the L group, treatment of statins markedly restored serum NOx level in the L1.0P100 and L1.0C2 groups (Figure 4B).

eNOS and iNOS protein expression was examined by Western blot analysis. Compared with the control group, aortic eNOS protein expression did not change in the L group (Figure 4C). In contrast, aortic eNOS protein level was significantly higher in the L1.0P100 and L1.0C2 groups than in the control or L groups (Figure 4C). Aortic iNOS protein expression could not be detected in any groups (data not shown). In the heart, there was no difference in eNOS protein expression between the control and L groups, Statins increased eNOS protein level in L-NAME–treated rats (Figure 4D). iNOS protein could not be detected in the heart of any groups (data not shown).

Immunohistochemical study showed strong iNOS inductions mainly in lesional inflammatory cells in the L group (Figure 1C). Statins markedly reduced such iNOS protein level as assessed by immunohistochemistry (Figure 1C). In contrast, endothelial NOS immunoreactivity in coronary arteries was similar in control and L group. Statins markedly increased eNOS immunoreactivity in the endothelial layer of coronary arteries (Figure 1C).

Effects of Statins on RhoA Membrane Translocation

Immunoblot for RhoA (a major isoform of Rho) in the membrane and cytosolic fraction of cardiac tissue exhibited that L-NAME significantly increased membrane translocation of RhoA on day 3. Cotreatment with statins significantly decreased membrane translocation of RhoA with a concomitant increase of RhoA in the cytosol (Figure 4E).

Effects of Statins on Vascular Remodeling on Day 28

The increases in medial thickening (the wall-to-lumen ratio) and perivascular fibrosis of coronary arteries seen in the L group was inhibited in the L1.0P100 and L1.0C2 groups (Figures 1B and 5). In addition, cardiac fibrosis was also inhibited in the L1.0P100 and L1.0C2 groups (data not shown).

Serum Statin Concentrations

Serum pravastatin concentration was 7.4±0.8 ng/mL in the L1.0P100 group. Serum maximum concentrations of pravastatin after oral administration at 20 mg in healthy human subjects are 26.1 to 38.4 ng/mL.22 Serum cerivastatin concentration was 2.1±3.1 ng/mL in the L1.0C2 group. Serum maximum concentrations of cerivastatin after oral administration at 0.3 or 0.4 mg in healthy human subjects are 3.7 and 6.3 ng/mL, respectively.23

Effects of High-Dose L-NAME on the Vasculoprotective Effects of Statins

To examine if the beneficial effects of statins are due to restoration of eNOS activity, we determined if the higher dose of L-NAME could block the vasculoprotective effects of statins. The higher dose of L-NAME suppressed statin-induced restora-
tion of NO production (Figure 4B), statin-induced inhibition of vascular inflammatory/proliferative changes (Figures 2E and 2F), and statin-induced inhibition of RhoA translocation to membrane (data not shown) on day 3 of L-NAME administration. The high dose of L-NAME did not affect eNOS expression in both the heart and aorta (data not shown). Also, the high dose of L-NAME attenuated statin-induced inhibition of vascular remodeling on day 28 (data not shown).

Discussion

We have demonstrated herein that (1) treatment with statins such as pravastatin and cerivastatin inhibits early vascular inflammation and (2) statins also inhibit proliferative changes and the development of cardiovascular remodeling in a rat model of chronic inhibition of NO synthesis. Importantly, such antiinflammatory and antiarteriosclerotic effects of statins cannot be attributed to their lipid-lowering effects.

We have recently reported that MCP-1 mediates early vascular inflammation and subsequent vascular medial thickening and that TGF-β1 mediates perivascular and myocardial fibrosis in our model. Our present observations suggest that treatment with statins reduced such pathological disorders by inhibiting gene expression and biological activity of MCP-1 and TGF-β1. Because restoration of endothelial NO-mediated vasodilation is an early event after cholesterol-lowering therapy with statins, we hypothesized that the beneficial effects of statins seen in this study involved the increase in NO synthase expression or activity. We found that treatment with statins augmented endothelial-type NO synthase protein expression and restored NO-generating capacity and serum NOx concentration. Such augmented endothelial NO synthase expression and activity are in agreement with prior in vitro studies that statins increased NO synthesis from the endothelial cells by increasing NO synthase mRNA stability. Therefore, statins are likely to restore the L-NAME–induced inhibition of endothelial NO synthase activity by augmenting NO synthase protein expression and thereby elicited antiinflammatory and antiarteriosclerotic actions in this model. Another several lines of evidence in our study may also support our hypothesis. We have demonstrated that the antiinflammatory and antiproliferative effects of statins in regular-dose L-NAME (1 mg/mL)–treated rats completely disappeared in rats treated with high-dose L-NAME (1.8 mg/mL) (Figures 2E and 2F). We have noticed that disappearance of the vasculoprotective effects of statins in high-dose L-NAME–treated rats corresponded to failure of restoration of NO production (Figure 4B), inhibition of vascular inflammatory/proliferative changes (Figures 2E and 2F), and inhibition of RhoA membrane translocation. These data substantially support the idea that the beneficial effects of statins observed in this model may be mediated at least in part by their effect on eNOS activity. Other possible mechanisms for vasculoprotective effects of statins, which were not investigated in the present study, include inhibition of

Figure 4. Effects of statins on NOx-generating capacity, serum NOx concentration, eNOS expression, and RhoA localization. A, Aortic NOx-generating capacity in the control, L, L1.0+P100, and L1.0+C2 groups. B, Serum NOx concentration in the control, L, L1.0+P100, L1.0+C2, L1.8+P250, and L1.8+C10 groups. C, Immunoblot analysis of eNOS in the aorta of the control, L, L1.0+P100, and L1.0+C2 groups. D, Immunoblot analysis of eNOS in the heart of the control, L, L1.0+P100, and L1.0+C2 groups. E, Immunoblot analysis of RhoA in the membrane and cytosolic fractions in the heart of the control, L, L1.0+P100, and L1.0+C2 groups. *P<0.05 vs L group; †P<0.05 vs control group. n=9 to 10.

Figure 5. Effect of statin administration on medial thickening (wall-to-lumen ratio) and perivascular fibrosis of coronary arteries on day 28. A, Wall-to-lumen ratio of coronary arteries. B, Perivascular fibrosis of coronary arteries. *P<0.05 vs L group; †P<0.05 vs control group. n=4 to 5.
oxidative stress, inflammatory cytokine activity, or matrix metalloproteinase activity.

Our present finding is also consistent with the recently clarified role of Rho GTPase in mediating cardiovascular disease.25 For example, Rho promotes cell-cycle progression and proliferation in vascular smooth muscle cells,26 which are central events in the pathogenesis of several vascular lesions; Rho also mediates the activation of the proinflammatory transcription factor nuclear factor-κB (NF-κB) in response to cytokines.27 Furthermore, Rho proteins may also be involved in mediating increases in oxidative stress.28

We next hypothesized that the increased NO synthase activity by statins might result from inhibition of small GTPase protein Rho activity. We could demonstrate in the present study that statins prevented the L-NAME–induced increase in Rho activation. Since angiotensin II has been shown to induce Rho activation in several cell types in vitro,29,30 the L-NAME–induced increase in Rho activation may be mediated by increased angiotensin II activity. Evidence suggests that the Rho pathway controls multiple cell functions such as adhesion, proliferation, migration, and the calcium sensitivity of the contractile proteins,31 and that blockade of the Rho pathway with C3 toxin may increase NO synthase protein expression in vitro24 and in vivo.32 Accordingly, these results suggest that treatment with statins augment endothelial type NO synthase activity at least in part by inhibiting Rho activation.

It is reported that treatment with statins lower blood pressure in hypertensive rats.33 Therefore, normalization of the L-NAME–induced hypertension by statins at the late stage seen in the present study (Table 1) may not be an extremely surprising finding. Because we previously demonstrated that normalization of L-NAME–induced hypertension by hydralazine treatment did not inhibit such pathological changes,11 it is unlikely that the antihypertensive effect of statins may contribute largely to the prevention of cardiovascular pathological changes. However, we cannot rule out the possibility that some of the beneficial effects of statins might have been due to normalization of blood pressure.

We previously demonstrated that the increased angiotensin II activity by overexpression of ACE mediates the cardiovascular pathological changes in this model. There was no significant difference in the enzyme activity between hearts from the L-NAME and L-NAME plus statin groups. Thus, it is likely that statins did not affect cardiac angiotensin II activity but inhibited inflammatory and proliferative disorders induced by increased angiotensin II activity in our experiments.

Although very high doses of statins (pravastatin at 100 mg/kg per day and cerivastatin at 2 mg/kg per day) were needed to inhibit early inflammation and late arteriosclerosis, serum concentrations of statins in our rat model were equivalent to those reported in humans.22,23 This discrepancy may be explained by more rapid metabolism of statins from circulation in rats.34,35 No serious side effects were observed by administration of such high doses of statins to rats. Thus, it is unlikely that vasculoprotective effects of statins seen in the present study resulted from clinically irrelevant serum concentrations.

In conclusion, this study has demonstrated direct antiinflammatory and antiarteriosclerotic effects of statins in a rat model of chronic inhibition of NO synthesis. Such vasculo-protective effects of statins are not likely to be mediated by their lipid-lowering actions but seem to be mediated by augmentation of endothelial-type NO synthase expression and activity by the inhibition of Rho activity. The observed vasculoprotective effects of statins are not related to hydrophilic versus lipophilic properties of statins, because both hydrophilic statin (pravastatin) and lipophilic statins (cerivastatin) exhibited similar effects. Recent clinical trials showed that reduction of ischemic cardiovascular events in patients after myocardial infarction by pravastatin therapy was related closely with the decrease in blood C-reactive protein levels.36 Pravastatin therapy reduced monocyte infiltration into atherosclerotic plaque and preserved endothelial functions in atherosclerotic monkeys.37 Such antiinflammatory effects of pravastatin are suggested to be a cholesterol-lowering independent action. The present study may provide a new aspect of how statins reduce cardiovascular ischaemic events.

Acknowledgments
This study was supported by Grants-in-Aid for Scientific Research (11470164, 11158216, 11557056, 10307019, and 10177226) from the Ministry of Education, Science and Culture, Tokyo, Japan.

References


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Circ Res. 2001;89:415-421; originally published online August 16, 2001;
doi: 10.1161/01.HHR.1701.096614

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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