HMG-CoA Reductase Inhibitors Improve Endothelial Dysfunction in Normocholesterolemic Hypertension via Reduced Production of Reactive Oxygen Species

Sven Wassmann, Ulrich Laufs, Anselm T. Bäumer, Kirsten Müller, Katja Ahlbory, Wolfgang Linz, Gabi Itter, Renate Rösen, Michael Böhm, Georg Nickenig

Abstract—3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) significantly reduce cardiovascular mortality associated with hypercholesterolemia. There is evidence that statins exert beneficial effects in part through direct effects on vascular cells independent of lowering plasma cholesterol. We characterized the effect of a 30-day treatment with atorvastatin in normocholesterolemic, spontaneously hypertensive rats (SHR). Systolic blood pressure was significantly decreased in atorvastatin-treated rats (184±5 versus 204±6 mm Hg for control). Statin therapy improved endothelial dysfunction, as assessed by carbachol-induced vasorelaxation in aortic segments, and profoundly reduced angiotensin II–induced vasoconstriction. Angiotensin type 1 (AT1) receptor, endothelial cell NO synthase (ecNOS), and p22phox mRNA expression were determined with quantitative reverse transcription–polymerase chain reaction. Atorvastatin treatment downregulated aortic AT1 receptor mRNA expression to 44±12% of control and reduced mRNA expression of the essential NAD(P)H oxidase subunit p22phox to 63±7% of control. Aortic AT1 receptor protein expression was consistently decreased. Vascular production of reactive oxygen species was reduced to 62±12% of control in statin-treated SHR, as measured with lucigenin chemiluminescence assays. Accordingly, treatment of SHR with the AT1 receptor antagonist fonsartan improved endothelial dysfunction and reduced vascular free-radical release. Moreover, atorvastatin caused an upregulation of ecNOS mRNA expression (138±7% of control) and an enhanced ecNOS activity in the vessel wall (209±46% of control). Treatment of SHR with atorvastatin causes a significant reduction of systolic blood pressure and a profound improvement of endothelial dysfunction mediated by a reduction of free radical release in the vasculature. The underlying mechanism could in part be based on the statin-induced downregulation of AT1 receptor expression and decreased expression of the NAD(P)H oxidase subunit p22phox, because AT1 receptor activation plays a pivotal role for the induction of this redox system in the vessel wall. (Hypertension. 2001;37:1450-1457.)

Key Words: statins ■ angiotensin ■ reactive oxygen species ■ endothelial dysfunction ■ rats, spontaneously hypertensive

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) decrease plasma cholesterol concentrations by blocking the key enzyme of cholesterol biosynthesis.1,2 The reduction of mortality and morbidity in hypercholesterolemic subjects3,4 has been attributed to the statin-mediated lowering of plasma cholesterol. However, the product of the enzyme reaction that is inhibited by statins, mevalonic acid, serves as a precursor to numerous isoprenoid metabolites.1 This may lead to the pleiotrophic effects of these drugs, and there is growing evidence that some beneficial effects of these agents may be independent of plasma cholesterol levels.5,6 Direct effects of statins on vascular cells could have important implications for the development of endothelial dysfunction, a prerequisite of atherosclerosis. Disruption of the delicate balance of the NO system, neurohormonal systems involving endothelin and angiotensin II, and especially the vascular production of reactive oxygen species (ROS) promotes the development of endothelial dysfunction.7 In this context, it has been reported that, for example, the NO and endothelin system may be directly influenced by statins.8,9 Of note, one of the key events in the regulation of vascular ROS production is the activation of the angiotensin type 1 (AT1) receptor expressed in vascular smooth muscle cells (VSMC), which leads to stimulation of the NAD(P)H oxidase, an enzyme responsible for the majority of ROS produced in the vessel wall, and to an enhanced expression of the essential p22phox subunit of this system.10–13
To further evaluate direct statin-mediated cellular effects, spontaneously hypertensive rats (SHR), an animal model with profound vascular dysfunction on the basis of hypertension in the absence of lipid disorders, were treated with atorvastatin. Experiments were developed to investigate the effects of atorvastatin on blood pressure, endothelial dysfunction, vasconstriction, vascular ROS production, and the decisive involvement of AT1 receptor regulation in this pathological setting.

**Methods**

**Materials**

Angiotensin II, lucigenin, Taq DNA polymerase, nucleotides, salts, and other chemicals were purchased from Sigma Chemical. Moloney murine leukemia virus reverse transcriptase was obtained from Gibco BRL. Nitroglycerin was purchased from Solvey. RNA clean was obtained from AGS. Atorvastatin was a gift of Gödecke-Parke-Davis (Freiburg, Germany). Fonsartan (HR 720) was a gift of Hoechst Marion Roussel (Frankfurt/Main, Germany).

**Animals**

Male SHR (Aventis Pharma) were put on a standard chow (Altromin Maintenance Diet 1320, Altromin) or on standard chow supplemented with atorvastatin, and they received drinking water ad libitum. The animals received atorvastatin at a dose of 50 mg/kg of body weight per day, which was calculated according to the daily food intake. In rats, this dose produces plasma concentrations that are comparable to those achieved after oral administration of common food intake. In rats, this dose produces plasma concentrations that are comparable to those achieved after oral administration of common.

**Aortic Ring Preparations and Tension Recording**

After excision of the descending aorta, the vessel was immersed in chilled, modified Tyrode buffer (pH 7.4; NaCl 136.9 mmol/L, KCl 5.4 mmol/L, CaCl2 1.8 mmol/L, MgCl2 1.05 mmol/L, NaEDTA 0.05 mmol/L, NaH2PO4 0.42 mmol/L, NaHCO3 22.6 mmol/L, and D(+)-glucose 5.5 mmol/L), which contained additional ascorbic acid (0.28 mmol/L) and indothemcin (0.01 mmol/L). Adventitial tissue was carefully removed. Five-millimeter rings were mounted for recording of isometric tension in organ baths filled with modified Tyrode buffer (37°C), which was continuously aerated with 95% O2 and 5% CO2. The preparations were attached to a force transducer, and isometric tension was recorded on a polygraph. Aortic rings were allowed to equilibrate for 60 minutes. A resting tension of 1g was maintained throughout the experiment. The following drugs were added in increasing concentrations to obtain cumulative concentration-response curves: KCl 20 and 60 mmol/L, angiotensin II 0.01 mmol/L to 1 μmol/L, phenylephrine 0.1 mmol/L to 10 μmol/L, carbachol 0.1 mmol/L to 100 μmol/L, and nitroglycerin 1 mmol/L to 10 μmol/L. The drug concentration was increased when vasoconstriction or vasorelaxation was completed (an average 3 to 6 minutes for each step). Drugs were washed out before the next substance was added.

**mRNA Isolation and Polymerase Chain Reactions**

Aortas were isolated, quickly frozen in liquid nitrogen, and homogenized with a motorized homogenizer. RNA was isolated with RNA clean, according to the manufacturer’s protocol, to obtain total cellular RNA. One-microgram aliquots were electrophoresed through 1.2% agarose to 0.67% formaldehyde gels and stained with ethidium bromide to verify the quantity and quality of the RNA. One microgram of the isolated total RNA and 10 pg of an AT1 receptor mutant mRNA were mixed and reverse transcribed. cDNA was amplified by polymerase chain reaction (PCR). Twenty-eight cycles were performed under the following conditions: 30 s, 94°C; 45 s, 55°C, and 45 s, 72°C. The sequence for AT1 receptor antisense primers was 5’-ACC-CTC-TAC-AGC-ATC-ATC-TTC-GTG-ATG-GGG-3’ and 5’-GGG-AGC-GTC-GAA-ATT-CGAC-GAC-TCA-TAA-TGA-3’, respectively. The same cDNA samples were used for GAPDH cDNA amplification (23 cycles) to confirm that equal amounts of RNA were reverse transcribed. The primers used were 5’-ACC-ACA-GTC-CAT-GCC-ATC-AC-3’ and 5’-TCC-ACC-CTG-TTG-CTG-3’. PCR amplification gave 479 bp, 191 bp, and 452 bp of fragments originated from AT1 receptor mRNA, mutated AT1 receptor mRNA, and GAPDH mRNA, respectively. Amplification of a 340-bp fragment of endothelial cell NO synthase (ecNOS) cDNA was performed with primer pairs 5’TTC-GCG-CTG-CCA-CCT-GAT-CCT-AA-3’ and 5’-AAC-ATA-TGT-CCT-TGC-TCA-AGG-CA-3’ for 35 cycles under the following conditions: 30 s, 94°C; 30 s, 60°C; and 60 s, 72°C. A 485-bp fragment of the NAD(P)H oxidase subunit p2phox was amplified using primers 5’-GAC-GCT-TCA-CCG-AGT-GGT-3’ and 5’-CAC-GAC-CTC-ATG-TGT-CAG-TCA-3’. Thirty cycles were performed under the following conditions: 60 s, 94°C; 60 s, 65°C; and 90 s, 72°C. For semiquantification, PCR conditions were chosen so that the reaction was within the linear exponential phase with respect to the amount of cDNA template and the number of cycles performed. Equal amounts of reverse transcription (RT)-PCR products were loaded on 1.5% agarose gels, and optical densities of ethidium bromide–stained DNA bands were quantified.

**Western Blot Analysis**

Aortas were isolated, quickly frozen in liquid nitrogen, and homogenized with a motorized homogenizer in ice-cold lysis buffer that contained additional leupeptin and aprotinin. Thereafter, membrane and cytosolic proteins were isolated by centrifugation (30 minutes, 48,000g, 4°C). Thirty-microgram aliquots of membrane proteins were electrophoresed through 0.1% SDS/10% polyacrylamide gels. Proteins were blotted to nitrocellulose membranes in a semidry blotting chamber (Pharmacia Biotech). Blot membranes were stained with ponceau red to verify appropriate protein transfer and equal loading for each lane. Immunoblotting was performed for 1 hour at 24°C using an AT1 receptor rabbit polyclonal IgG antibody (1:250 dilution; sc 1173, AT; [N-10], Santa Cruz Biotechnology Inc, Santa Cruz, Calif). Immunodetection was accomplished with a goat anti-rabbit secondary antibody for 30 minutes at 24°C (1:5000 dilution). Immunoblotting was performed for 1 hour at 24°C using an AT1 receptor rabbit polyclonal IgG antibody (1:250 dilution; sc 1173, AT; [N-10], Santa Cruz Biotechnology Inc, Santa Cruz, Calif). Immunodetection was accomplished with a goat anti-rabbit secondary antibody for 30 minutes at 24°C (1:5000 dilution, Sigma Chemical) and with the enhanced chemiluminescence kit (Amersham). Autoradiography was performed at 24°C.

**Measurement of Superoxide Release**

Aortas were carefully excised and placed in chilled, modified Krebs-HEPES buffer (pH 7.4; NaCl 99.01 mmol/L, KCl 4.69 mmol/L, CaCl2 1.87 mmol/L, MgSO4 1.20 mmol/L, NaH2PO4 0.42 mmol/L, NaHCO3 22.6 mmol/L, and D(+)-glucose 5.5 mmol/L), which contained additional ascorbic acid (0.28 mmol/L) and indothemcin (0.01 mmol/L). Adventitial tissue was carefully removed. Five-millimeter rings were mounted for recording of isometric tension in organ baths filled with modified Tyrode buffer (37°C), which was continuously aerated with 95% O2 and 5% CO2. The preparations were attached to a force transducer, and isometric tension was recorded on a polygraph. Aortic rings were allowed to equilibrate for 60 minutes. A resting tension of 1g was maintained throughout the experiment. The following drugs were added in increasing concentrations to obtain cumulative concentration-response curves: KCl 20 and 60 mmol/L, angiotensin II 0.01 mmol/L to 1 μmol/L, phenylephrine 0.1 mmol/L to 10 μmol/L, carbachol 0.1 mmol/L to 100 μmol/L, and nitroglycerin 1 mmol/L to 10 μmol/L. The drug concentration was increased when vasoconstriction or vasorelaxation was completed (an average 3 to 6 minutes for each step). Drugs were washed out before the next substance was added.
Lipid Profile in Atorvastatin-Treated SHR and Control Animals

<table>
<thead>
<tr>
<th>Cholesterol, mg/dL</th>
<th>Statin, mg/dL</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>Statin</td>
</tr>
<tr>
<td>89±8</td>
<td>60±5*</td>
</tr>
<tr>
<td>HDL</td>
<td>48±2</td>
</tr>
<tr>
<td>37±2*</td>
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</tr>
<tr>
<td>LDL</td>
<td>27±4</td>
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<tr>
<td>14±4*</td>
<td></td>
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<tr>
<td>Triglycerides</td>
<td>72±15</td>
</tr>
<tr>
<td>48±16*</td>
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Plasma concentrations of total cholesterol, LDL, HDL, and triglycerides were determined after the experimental treatment period. Data are expressed as mean±SEM (n=5 per group). 

*P<0.05 vs control.

ecNOS Activity Assay

Excised aortic segments were immersed in ice-cold homogenization buffer that contained 250 mmol/L Tris/HCl, pH 7.4, 10 mmol/L EDTA, and 10 mmol/L EGTA and were mechanically homogenized. ecNOS activity was determined in 10-µg protein aliquots by measuring the conversion of [3H]-arginine to [3H]-citrulline using a NOS assay kit from Calbiochem. Rat cerebellum extracts, containing elevated amounts of neuronal NOS, were used as positive controls, whereas aortic lysates incubated in the presence of Nω-nitro-L-arginine methyl ester (L-NAME) served as blanks. The amount of [3H]-citrulline was quantified with a β-counter (Beckman).

Statistical Analysis

Data are presented as mean±SEM obtained in at least 4 separate experiments. Statistical analysis was performed by ANOVA and Mann-Whitney U test. P<0.05 indicates statistical significance.

Results

Lipid Profiles in SHR

Table 1 displays plasma concentrations of total cholesterol, LDL, HDL, and triglycerides in the animals after the experimental treatment period (n=5 per group). All parameters were measured within the normal range in the control group. Statin treatment led to a significant reduction of the plasma concentrations of triglycerides, cholesterol, LDL, and HDL (P<0.05 versus control).

Effect of Atorvastatin on Blood Pressure in SHR

Systolic blood pressure evaluated with the tail-cuff method was measured before and after treatment in the statin and control group. Before treatment, blood pressure was similar in both groups and was pathologically elevated. Treatment with atorvastatin caused a significant reduction of blood pressure levels as depicted in Figure 1. Systolic blood pressure was 104±6 mm Hg in control animals and 184±5 mm Hg in statin-treated rats (n=10 per group; P<0.05 versus control). Heart rate remained unchanged (392±8 versus 405±9 bpm for control; ns).

Effect of Atorvastatin on Vasorelaxation and Vasoconstriction

The reduction of blood pressure could be related to a statin-induced improvement of vasorelaxation and to reduced vasoconstriction. To test this possibility, aortic rings were isolated and their functional performance was assessed in organ chamber experiments (n=6 with 18 rings per group). Figure 2A and 2B show the endothelial cell-dependent vasorelaxation on increasing concentrations of carbachol and the endothelial cell-independent relaxation exerted by nitro-
glycerin. Whereas the endothelial cell-independent vasorelaxation was not altered by the treatment with atorvastatin, the HMG-CoA reductase inhibitor markedly increased the carbachol-induced vasodilatation, which suggested a significant improvement of endothelial dysfunction in SHR through atorvastatin (force of contraction 14±2% versus 32±3% for control of phenylephrine-induced vasoconstriction; carbachol 100 µmol/L; P<0.05 versus control).

The contraction of the aortas from control animals and statin-treated rats was assessed during exposure to increasing concentrations of either phenylephrine or angiotensin II. Figure 2C and 2D reveal that the angiotensin II–induced vasoconstriction was selectively decreased after treatment with atorvastatin (force of contraction 4.4±0.5% versus 8.2±0.9% for control of KCl-induced vasoconstriction; angiotensin II 1 µmol/L; P<0.05 versus control). In contrast, α-adrenoceptor–mediated constriction induced by phenylephrine was not significantly altered. In addition, vasoconstriction induced by KCl was identical in both groups (data not shown).

Effect of Atorvastatin on Vascular Production of ROS

The decreased vascular responsiveness on angiotensin II in the statin-treated group could also lead to a decreased level of free radicals in the vessel wall. This could have an impact on vascular function and explain the improvement of endothelial dysfunction. Therefore, the vascular production of ROS was assessed by lucigenin chemiluminescence assays in isolated aortic segments of control and statin-treated SHR. Figure 3A illustrates that treatment with atorvastatin caused a significant decrease of superoxide production in the vessel wall to 62±12% of control levels (n=6 per group; P<0.05 versus control).

Effect of Atorvastatin on Vascular NAD(P)H Oxidase Expression

To measure NAD(P)H oxidase expression in the vessel wall, the essential subunit of the enzyme in this tissue, p22phox, was quantified on mRNA level via semiquantitative RT-PCR methodology. Figure 3B and 3C show a representative agarose gel and the densitometric analysis of the amplified...
p22phox PCR fragments (n=5 per group). Atorvastatin caused a reduction of p22phox mRNA expression to 63±8% compared with control animals (P<0.05 versus control).

Effect of Atorvastatin on Vascular AT₁ Receptor Expression
Statin therapy of SHR caused a reduction of angiotensin II–induced vasoconstriction and a decrease of vascular ROS production. Both effects are mediated through AT₁ receptor activation. Therefore, it was reasonable to assume that atorvastatin directly influenced vascular AT₁ receptor expression. Vascular AT₁ receptor mRNA concentrations were assessed by means of quantitative RT-PCR in RNA isolated from aortic segments of both SHR groups. Figure 4A shows a representative ethidium bromide–stained agarose gel of a PCR reaction that illustrates amplified DNA fragments generated from wild-type AT₁ receptor mRNA and from mutated AT₁ receptor mRNA that served as internal standard. Figure 4B demonstrates the densitometric analysis (n=5 per group) that revealed that AT₁ receptor mRNA expression was significantly downregulated to 44±13% in SHR treated with atorvastatin (P<0.05 versus control). This reduced expression of vascular AT₁ receptor mRNA was translated to a marked decrease in AT₁ receptor protein expression in the vasculature of statin-treated SHR, as demonstrated in a representative immunoblot in Figure 4C.

Effect of Atorvastatin on Vascular ecNOS mRNA Expression and ecNOS Activity
In addition, ecNOS and GAPDH mRNA expression were assessed in the same aortic tissue samples via semiquantitative RT-PCR. A representative agarose gel is shown in Figure 5A. Figure 5B illustrates the densitometric results of these experiments (n=4 per group). While GAPDH expression remained unchanged between groups, ecNOS mRNA expression was upregulated in aortas of statin-treated SHR to 138±7% of control levels (P<0.05 versus control).

Because ecNOS expression was upregulated by statin treatment, the effect of atorvastatin on ecNOS activity was assessed in homogenates of isolated aortic segments with an [³H]-arginine-citrulline conversion assay. Figure 5C shows that ecNOS activity was increased by 2-fold in the atorvastatin-treated group (209±46% of control; n=4 per group; P<0.05 versus control).

Effect of AT₁ Receptor Blockade on Aortic Vasorelaxation and Production of ROS
To confirm the hypothesis that statin-mediated AT₁ receptor downregulation that leads to reduced ROS production demonstrates an important mechanism underlying the improved endothelial dysfunction after statin treatment, the effect of an AT₁ receptor antagonist fonsartan (HR 720; 10 mg/kg of body weight per day) for 30 days. After treatment, systolic blood pressure was 135±6 mm Hg in this group (n=6; P<0.05 versus control).

Aortic rings were isolated, and vasorelaxation and vasoconstriction were assessed in organ chamber experiments (n=6 with 12 rings per group). Figure 6A shows the endothelial cell-dependent vasorelaxation on stimulation with carbachol and demonstrates that treatment with the AT₁ receptor antagonist fonsartan (100 μmol/L; P<0.05 versus control). Endothelial cell-independent vasorelaxation exerted by nitroglycerin was not altered compared with control animals (data not shown). As expected, angiotensin II–induced vasoconstriction was markedly reduced after treatment with fonsartan, whereas phenylephrine- and KCl-driven vasoconstriction remained unchanged compared with untreated SHR (data not shown).

In addition, the production of ROS in isolated aortic segments was determined with lucigenin chemiluminescence assays. Figure 6B illustrates that treatment with the AT₁
receptor antagonist caused a profound reduction of superoxide production in the vessel wall to 33±67% of control levels (n=56 per group; P<0.05 versus control).

Discussion

Our findings indicate that atorvastatin decreases vascular AT1 receptor expression that leads to reduced production of ROS, improved endothelial function, decreased angiotensin II–driven vasoconstriction, and lowering of blood pressure in normocholesterolemic SHR. In addition, statin treatment causes upregulation of vascular ecNOS expression and enhancement of ecNOS activity.

We propose that the statin-induced downregulation of AT1 receptor expression in vivo is one of the initial and essential steps for the observed beneficial effects of statin treatment in the tested experimental model of SHR. Namely, AT1 receptor activation causes vasoconstriction, which is closely related to blood pressure regulation.16 Thus, diminished AT1 receptor expression in the vessel wall may cause decreased vasoconstriction and blood pressure reduction, as found in our model. Reduction of aortic AT1 receptor expression by 50% in the statin-treated rats correlates with the improvement of carbachol-mediated vasodilatation (30% versus 15% of phenylephrine-induced tension) and with the 40% decrease in vascular superoxide release. AT1 receptor activation plays a key role in the vascular production of ROS.10 These free radicals are thought to have great implications for the pathogenesis of hypertension and atherosclerosis.7,17 Especially, angiotensin II–driven hypertension is almost exclusively dependent on ROS production.11,12,18 Furthermore, free radicals are involved in vascular cell growth, apoptotic processing, cytotoxic effects, and in the development of endothelial dysfunction.19,20 To date, it is believed that increased amounts of free radicals scavenge the vasorelaxing nitric oxide, causing impaired endothelial-dependent vasodilatation.7 Endothelial dysfunction is a characteristic of early stages of atherosclerosis, which can be induced by various disorders such as hypertension, diabetes, smoking, and hypercholesterolemia.21,22

In the latter respect, it is not surprising that cholesterol-lowering through statin therapy is known to improve endothelial dysfunction.23 Our data show that atorvastatin treatment leads to a significant reduction of plasma lipid concentrations in normocholesterolemic rats. However, SHR develop endothelial dysfunction because of severe hypertension, whereas lipid disorders are not involved in this pathological setting. Even high-cholesterol concentrations in the diet of SHR produce only moderate increases of plasma cholesterol concentrations. Although atorvastatin caused a
reduction of total and LDL cholesterol levels, it seems unlikely that this effect accounts for the aforementioned modulations of vascular function, because LDL levels were low before treatment and were decreased only by \(13\) mg/dL. In contrast, in hypercholesterolemic animal models, effects on AT1 receptor expression and endothelial function were observed after an increase of plasma cholesterol concentrations by more than 25-fold.\(^{17,24}\) In addition, vasoprotective HDL cholesterol was also decreased by atorvastatin in our model. However, a contribution of the lowered lipid levels to the improved endothelial function in the statin-treated rats cannot be excluded.

We found a decreased vascular production of free radicals and an improved endothelial dysfunction in the statin-treated SHR. In addition to the reduction of AT1 receptor expression, a statin-mediated upregulation of vascular ecNOS expression was detected, which is in agreement with previous in vitro and in vivo studies.\(^{9,25}\) Furthermore, ecNOS activity was upregulated in these aortas, which may result in an increased production of NO. The enhanced bioavailability of NO also contributes to the improvement of endothelial dysfunction.

However, it may be assumed that atorvastatin has a major impact on the improvement of endothelial dysfunction in SHR via the reduced production of ROS initiated by the statin-induced downregulation of vascular AT1 receptor expression, because stimulation of this receptor leads to an increase of free radical production.\(^{10}\) This hypothesis is strengthened by the fact that treatment of SHR with an AT1 receptor antagonist exerted a normalization of the endotheli- um-dependent vasodilatation and a profound reduction of free radical release in the vessel wall. Because the stimulation of the AT1 receptor by angiotensin II leads not only to direct activation of the superoxide-generating NAD(P)H oxidase but also to an enhanced expression of the essential p22phox subunit of this enzyme,\(^{12,13}\) the decreased expression of p22phox in aortas of SHR treated with atorvastatin may well contribute to the observed reduction of ROS production. The importance of AT1 receptor regulation for the development and progression of atherosclerosis and endothelial dysfunction is supported by the results of many studies investigating the effect of AT1 receptor activation and antagonism on several cellular and vascular parameters.\(^{17,26–33}\) Recently, it was demonstrated that AT1 receptor antagonism inhibits fatty streak formation in the aorta of hypercholesterolemic monkeys without alterations of blood pressure or lipid levels.\(^{34}\)

The presented data reveal that in addition to their cholesterol-lowering properties,\(^{2}\) statins exert various direct effects on cellular function. Other potentially important effects of statins include, for example, reduction of endothelin-1 and MCP-1 synthesis,\(^{8,35}\) inhibition of migration of monocytes,\(^{36}\) modification of the inflammatory response of macrophages...
and endothelial cells, suppression of ICAM-1 expression and enhancement of the fibrinolytic activity in endothelial cells, and inhibition of cell proliferation of VSMC. The molecular mechanisms by which HMG-CoA reductase inhibitors influence vascular cells and specifically downregulate AT1 receptor mRNA expression are only partially understood. Regulation of AT1 receptor expression may in part be mediated through cAMP-, MAP kinase-, or cytosolic calcium-dependent pathways. It is possible that statin-induced downregulation of AT1 receptor expression involves similar intracellular transduction mechanisms. In hypercholesterolemia, AT1 receptors are overexpressed, which can be reversed through lipid lowering by statins. However, in addition to cholesterol reduction, statins inhibit HMG-CoA reductase, which causes a decreased mevalonate synthesis beyond the lowering of plasma cholesterol. If confirmed in beneficial therapeutic effects observed with statins that are potentially associated with the attenuation of vasomotor tone. 

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