Atorvastatin Prevents Angiotensin II–Induced Vascular Remodeling and Oxidative Stress

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Abstract—Angiotensin II (Ang II) modulates vasomotor tone, cell growth, and extracellular matrix deposition. This study analyzed the effect of atorvastatin in the possible alterations induced by Ang II on structure and mechanics of mesenteric resistance arteries and the signaling mechanisms involved. Wistar rats were infused with Ang II (100 ng/kg per day, SC minipumps, 2 weeks) with or without atorvastatin (5 mg/kg per day). Ang II increased blood pressure and plasmatic malondialdehyde levels. Compared with controls, mesenteric resistance arteries from Ang II–treated rats showed the following: (1) decreased lumen diameter; (2) increased wall/lumen; (3) decreased number of adventitial, smooth muscle, and endothelial cells; (4) increased stiffness; (5) increased collagen deposition; and (6) diminished fenestrae area and number in the internal elastic lamina. Atorvastatin did not alter blood pressure but reversed all of the structural and mechanical alterations of mesenteric arteries, including collagen and elastin alterations. In mesenteric resistance arteries, Ang II increased vascular $O_2^{\cdot -}$ production and diminished endothelial NO synthase and CuZn/superoxide dismutase but did not modify extracellular-superoxide dismutase expression. Atorvastatin improved plasmatic and vascular oxidative stress, normalized endothelial NO synthase and CuZn/superoxide dismutase expression, and increased extracellular-superoxide dismutase expression, showing antioxidant properties. Atorvastatin also diminished extracellular signal–regulated kinase 1/2 activation caused by Ang II in these vessels, indicating an interaction with Ang II–induced intracellular responses. In vascular smooth muscle cells, collagen type I release mediated by Ang II was reduced by different antioxidants and statins. Moreover, atorvastatin downregulated the Ang II–induced NADPH oxidase subunit, Nox1, expression. Our results suggest that statins might exert beneficial effects on hypertension-induced vascular remodeling by improving vascular structure, extracellular matrix alterations, and vascular stiffness. These effects might be mediated by their antioxidant properties. **(*Hypertension*. 2009;54:142-149.)**

Key Words: angiotensin II ■ atorvastatin ■ extracellular matrix ■ remodeling ■ oxidative stress

Hypertension is associated with structural changes (vascular remodeling) of resistance arteries like media thickening, reduced lumen diameter, and increased media:lumen ratio.[1–3] Among the cellular processes underlying these events, alterations in cell growth, migration, differentiation, and increased extracellular matrix (ECM) deposition have been described.[1,3] Angiotensin II (Ang II) influences the architecture and integrity of the vascular wall by modulating cell growth and regulating ECM composition.[1,2,4] Ang II mediates many of its cellular actions by stimulating the formation of reactive oxygen species (ROS), which play an important role in modulating inflammatory reactions.[1] Evidence from the last few years has suggested that increased oxidative stress plays a pathophysiological role in cardiovascular disease, including atherosclerosis, hypertension, and heart failure.[5–7] In fact, ROS have been shown to play a critical role in hypertrophy, fibrosis, and remodeling in the heart and vasculature.[6,8,9]

Statins are inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A reductase, a ubiquitous enzyme critical for the biosynthesis of cholesterol. Several clinical trials have demonstrated that statins exert beneficial effects in patients at high cardiovascular risk.[10] Moreover, several studies have shown that statins decrease blood pressure in variable degrees both in humans[11–14] and in experimental models,[15,16] although a lack of effect of statins on blood pressure levels has also been described.[17–19] Most of the benefits of statin therapy are attributable to the lowering of serum cholesterol levels. However, by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, statins can also inhibit the synthesis of isoprenoids, which are important lipid attachments for intracellular signaling molecules, eg, Rho and Rac. Thus, statins exert many effects beyond cholesterol lowering, including improvement of endothelial function, decreasing of vascular inflammation, inhibition of smooth muscle proliferation, and

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