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Angiotensin II, atherosclerosis, and aortic aneurysms

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Commentary

The importance of angiotensin II (Ang II) in the pathogenesis of cardiovascular disease has become increasingly clear as evidence has mounted for the clinical benefits of angiotensin-converting enzyme (ACE) inhibitors. Three pivotal heart failure trials in the 1980s (CONSENSUS, SOLVED, and SAVE) showed significantly increased survival among subjects treated with ACE inhibitors rather than conventional therapy. An interesting aspect of these trials was a 25% decrease in myocardial infarctions, suggesting that inhibition of the renin-angiotensin-aldosterone system (RAAS) by these drugs prevents atherosclerosis (1). Recently, the HOPE trial showed forcefully that chronic ACE inhibition can reduce cardiovascular events in patients with multiple risk factors for atherosclerosis (2). In this issue of the JCI, Daugherty et al. (3) provide exciting insights into potential relationships between Ang II, atherosclerosis, and aortic aneurysm formation. These authors studied the effects of Ang II in apoE–/– mice, which have increased total cholesterol and VLDL/LDL levels and develop spontaneous atherosclerosis even when fed a low-fat, low-cholesterol diet (4). Ang II infusion dramatically promoted vascular pathology, including an increase in the extent of atherosclerosis, a change in the nature of lesions and surrounding adventitial tissue, and formation of large abdominal aortic aneurysms. Furthermore, since atherosclerosis and aneurysm formation were not observed in strain matched apoE+/+ mice, Ang II's effects evidently depend on the hyperlipidemic state. Because Ang II […]

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The importance of angiotensin II (Ang II) in the pathogenesis of cardiovascular disease has become increasingly clear as evidence has mounted for the clinical benefits of angiotensin-converting enzyme (ACE) inhibitors. Three pivotal heart failure trials in the 1980s (CONSENSUS, SOLVED, and SAVE) showed significantly increased survival among subjects treated with ACE inhibitors rather than conventional therapy. An interesting aspect of these trials was a 25% decrease in myocardial infarctions, suggesting that inhibition of the renin-angiotensin-aldosterone system (RAAS) by these drugs prevents atherosclerosis (1). Recently, the HOPE trial showed forcefully that chronic ACE inhibition can reduce cardiovascular events in patients with multiple risk factors for atherosclerosis (2).

In this issue of the *JCI*, Daugherty et al. (3) provide exciting insights into potential relationships between Ang II, atherosclerosis, and aortic aneurysm formation. These authors studied the effects of Ang II in *apoE*$^{-/-}$ mice, which have increased total cholesterol and VLDL/LDL levels and develop spontaneous atherosclerosis even when fed a low-fat, low-cholesterol diet (4). Ang II infusion dramatically promoted vascular pathology, including an increase in the extent of atherosclerosis, a change in the nature of lesions and surrounding adventitial tissue, and formation of large abdominal aortic aneurysms. Furthermore, since atherosclerosis and aneurysm formation were not observed in strain matched *apoE*$^{+/+}$ mice, Ang II's effects evidently depend on the hyperlipidemic state.

Because Ang II infusion does not cause hypertension in mice, the effects of this factor on vascular pathology must be direct and independent of changes in blood pressure. How, then, does Ang II increase vascular pathology in hyperlipidemia? The answer is that Ang II acts on multiple cell types — endothelial cells, smooth muscle cells, monocytes, and lymphocytes — and promotes an inflammatory reaction in the vessel wall. Mediating the effects of Ang II, most likely, is monocyte chemoattractant protein-1 (MCP-1), a product of endothelial and smooth muscle cells, whose expression is induced by Ang II. Deficiency of the major MCP-1 receptor (CCR2) reduces atherosclerosis in the *apoE*$^{-/-}$ mouse (5), so it appears that Ang II increases inflammation and stimulates atherosclerosis by stimulating MCP-1 expression. A key future experiment will be to study the effects of Ang II in a *CCR2*$^{-/-}$, *apoE*$^{-/-}$ mouse.

Ang II is known to induce VCAM-1 expression by activating NF-κB–dependent gene expression (6), and it probably induces MCP-1 expression by a similar mechanism. In addition, Ang II stimulates production of reactive oxygen species (ROS) by inducing a vascular NADH oxidase (7), possibly through its specific effects on expression or activity of Mox1, a subunit of the vascular smooth muscle cell NADH oxidase (8). Induction of vascular ROS by Ang II appears in rodent models to be significantly greater than by other vasoconstrictors, such as norepinephrine (9). Thus, it is logical to propose that Ang II promotes atherosclerosis by two redox mechanisms: first, by increasing levels of lipid-oxidizing ROS, which promote the loading of lipid into foam cells; and second, by inducing the expression of redox-sensitive gene products, such as VCAM-1 and MCP-1.

> Perhaps the most interesting aspect of the present study was the appearance of aneurysms in the Ang II–treated mice.

Another important mechanism by which Ang II promotes atherosclerosis is endothelial dysfunction, measured by impaired vasorelaxation in response to acetylcholine. Ang II causes endothelial dysfunction in animal models (9), and ACE inhibitors improve endothelial dysfunction in patients with coronary artery disease (10). While endothelial dysfunction may be in part related to a change in vascular redox state that decreases nitric oxide bioavailability, other aspects of endothelial dysfunction may represent more direct effects of Ang II. Both VCAM-1 (6) and PAI-1 (11) are induced by this factor, and both of these proteins promote inflammation and thrombosis. Perhaps of greater consequence is the recently demonstrated effect of Ang II on endothelial cell apoptosis (12). Clearly, endothelial apoptosis must have still more dramatic effects on binding of platelets and inflammatory cells than does endothelial dysfunction. The exciting possibility that the proapoptotic effects of Ang II are augmented in *apoE*$^{-/-}$ mice must await future studies.

Perhaps the most interesting aspect of the present study was the appearance of aneurysms in the Ang II–treated mice. Aortic aneurysms are characterized by weakening, dilation, and occasional rupture of the vessel wall. Development of aneurysms is associated with inflammation, tissue remodeling, and upregulation of matrix-degrading proteinases, and it correlates with atherosclerosis, aging, pulmonary emphysema, and high blood pressure (13, 14). Matrix metalloproteinases (MMPs) can degrade a variety of extracellular matrix (ECM) molecules (15), and increased levels of MMP-2 (gelatinase A), MMP-9 (gelatinase B), and MMP-12 (macrophage elastase) have been found in the aneurysmal vessel wall (14, 16). Conversely, inhibitors of MMPs have been shown to prevent aneurysmal degeneration and rupture in animal models

(17, 18). These data indicate that degradation of ECM molecules is a critical event leading to weakening of the vessel wall. It is also possible that fragments of ECM proteins, released by proteolysis, contribute to matrix remodeling during aneurysm development by upregulating production of MMPs, serving as chemoattractants for monocytes and macrophages, or altering cell growth responses.

Several previous studies have also linked Ang II to aneurysm formation. Thus, Huang et al. showed that ACE inhibitors exert beneficial effects in a rat aneurysm model (19), and Nishijo et al. found that Ang II stimulated aneurysm formation in hypertensive mice (20). Ang II may promote development of aneurysms by contributing to the inflammatory response in the vessel wall — as seen in the present study (3) — or may act by altering smooth muscle cell migration (21), inducing ECM and MMP production (22–24), or stimulating ROS formation (25). In summary, the present study by Daugherty et al. provides additional rationale for inhibiting the RAAS to limit the progression of atherosclerosis; it also suggests benefits for ACE inhibition in peripheral vascular disease and aortic aneurysms, as well as coronary artery disease and myocardial infarction.

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