AT₁ Receptor Blockade and Atherosclerosis
Hopeful Insights Into Vascular Protection

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Angiotensin II (Ang II) is a potent vasoconstrictor, and apart from its effects on blood pressure, this short-lived peptide has been strongly implicated in the pathogenesis of ischemic cardiovascular disease. At the molecular and cellular levels, Ang II promotes a complex array of effects that may promote the initiation and progression of atherosclerosis. Within the last 2 years, a new receptor, a vascular protective molecule that retards the development of biological ramifications, because NO is widely considered a tion of nitric oxide (NO). The loss of NO has many vascular effects that may promote the initiation and progression of atherosclerosis. Many of the proatherosclerotic effects of Ang II are mediated by the binding of the peptide to the type 1 angiotensin (AT₁) receptor. In this issue of Circulation, Strawn and colleagues12 describe the effects of the AT₁ receptor antagonist losartan on the development of atherosclerosis in cholesterol-fed cynomolgus monkeys. Animals were fed an atherogenic diet for a total of 20 weeks. Starting in week 12 of the study, animals were randomly assigned treatment to losartan or vehicle control delivered by osmotic minipumps implanted subcutaneously. At the end of the study period (20 weeks), the animals were killed, and the extent of atherosclerosis was determined by classic methods. Losartan had a consistent effect on reducing the extent of fatty streak formation by ~50% in the aorta. The coronary arteries of losartan-treated animals also exhibited reduced arterial thickness. This reduction in the development of vascular pathology was not attributable to a decrease in plasma cholesterol. Furthermore, although losartan is primarily used for the treatment of hypertension in humans, these rather dramatic effects on the extent of fatty streak formation were not accompanied by a reduction in blood pressure in losartan-treated animals.

The present study confirms and extends prior observations made in a variety of experimental models indicating that interruption of the renin-angiotensin system can forestall the development of atherosclerosis. This was first shown with the ACE inhibitor captopril in Watanabe heritable hyperlipidemic rabbits.13 Subsequently, similar results have been reported in other animal models of atherosclerosis, including genetically modified mice,14 as well as rabbits15 and monkeys16 fed an atherogenic diet. The present study suggests that AT₁ receptor blockade blunts the development of atherosclerosis in the absence of a blood pressure–lowering effect. This finding contradicts prior studies in rabbits17 indicating that the antiatherosclerotic effects of ACE inhibition or AT₁ receptor blockade were dependent on blood pressure reduction. The reasons for this discrepancy are unclear but may reflect differences in animal models, pharmacological properties of the agents used, or other unidentified factors.

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At each of the well-defined stages of atherosclerosis, Ang II has the potential to contribute to the vascular pathobiology. For example, type 1 atherosclerotic lesions are defined by the presence of increased numbers of macrophages in the vascular intima and by the formation of foam cells.1 At this early stage of atherosclerosis, Ang II facilitates the recruitment of monocytes/macrophages into the vessel wall by stimulating the production of monocyte chemoattractant protein2 and vascular cell adhesion molecule-13 by smooth muscle cells. Once monocytes are localized to the blood vessel wall, these cells undergo a phenotypic transformation and take up oxidized LDL, leading to foam cell formation. Ang II indirectly facilitates this step by activating membrane-based NADP/NADPH oxidase,4 which promotes the production of superoxide radicals (O₂⁻). The oxidant stress triggered by Ang II may contribute to enhanced oxidation of LDL and degradation of nitric oxide (NO). The loss of NO has many vascular biological ramifications, because NO is widely considered a vascular protective molecule that retards the development of atherosclerosis.5 Within the last 2 years, a new receptor, biochemically distinct from the scavenger receptor, has been identified that mediates the binding and uptake of oxidized LDL (oxLDL) by vascular tissue. The expression of this oxLDL receptor has recently been shown to be regulated by Ang II,7 and this may contribute to endothelial dysfunction and to accumulation of lipid in atherosclerotic plaques. Later stages of atherosclerosis are characterized by increased smooth muscle cell content, increased matrix deposition, and the accumulation of fibrinogen and fibrin in the plaque.8 The pluripotent peptide Ang II likely contributes to all of these processes as well. Ang II is a well-characterized mitogen for vascular smooth muscle cells and stimulates the accumulation of extracellular matrix directly and indirectly by stimulating the production of transforming growth factor-β.9 Studies from this laboratory and others have shown that Ang II can promote the production of plasminogen activator inhibitor-1 in vascular tissue.10,11 This leads to reduced efficiency of the fibrinolytic system and likely contributes to the deposition of fibrin and fibrinogen typically seen in the late stages of atherosclerosis.
suggests that in primates, Ang II plays a role in atherosclerosis in the absence of hypertension.

If the same relationship holds true in humans, then we might expect to see clinical benefits from ACE inhibitors and AT1 receptor blockers in the prevention of ischemic cardiovascular events. Certainly, the Survival And Ventricular Enlargement (SAVE)18 and Studies Of Left Ventricular Dysfunction (SOLVD)19 trials suggested that the long-term administration of ACE inhibitors to patients with left ventricular dysfunction reduced the incidence of recurrent myocardial infarction. Whether or not interruption of the renin-angiotensin system reduces the incidence of myocardial infarction or cardiovascular death in normotensive subjects with preserved ventricular function is the subject of intense speculation at present. The recently reported results of the Heart Outcomes Prevention Evaluation (HOPE) trial demonstrate that ACE inhibition reduces the rates of death, myocardial infarction, and stroke in a high-risk population.20 The study by Strawn and colleagues12 suggests that clinical trials designed to test the hypothesis that AT1 receptor blockade retards the development of atherosclerosis in humans deserve to be performed.

References

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