Editorial Comment

Angiotensin II Type 1 (AT1) Receptor Deficiency Halts the Progression of Age-Related Atherosclerosis in Hypercholesterolemia: Molecular Link between the AT1 Receptor and Hypercholesterolemia

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Angiotensin II (Ang II), the major effector of the renin-angiotensin system (RAS), is a multifunctional peptide that modulates blood pressure, water and sodium homeostasis, and neurohumoral systems (1–3). The effects of Ang II are mediated by two plasma membrane receptors referred to as the Ang II type 1 (AT1) receptor and Ang II type 2 (AT2) receptor subtypes (1). In adult tissues, most of the known functions of Ang II are related to AT1 receptor activation, which plays an important role in the pathogenesis of cardiovascular diseases. In vascular cells, AT1 receptor activation by Ang II also leads to excessive production of reactive oxygen species (ROS), which is linked to activation of NAD(P)H oxidase (2, 3), and to the hypertrophy, proliferation, migration, and apoptosis of vascular cells. AT1 receptor-induced oxidative stress may cause nitric oxide (NO) inactivation, lipid oxidation, and activation of redox-sensitive genes such as chemotaxis and adhesion molecules, pro-inflammatory cytokines, and matrix metalloproteinases, all of which are involved in the initiation and progression of endothelial dysfunction and atherosclerosis. Many agonists, such as Ang II, growth factors, low-density lipoprotein (LDL) cholesterol, insulin, glucose, estrogen, progesterone, ROS, cytokines, and NO, are also known to modulate AT1 receptor expression in vascular cells (2, 3).

Hypercholesterolemia, in particular the elevation of plasma

LDL cholesterol concentrations, is associated with enhanced vascular AT1 receptor expression (3–5). Ang II stimulation of macrophage cholesterol biosynthesis is related to its interaction with the AT1 receptor and is followed by stimulation of macrophage 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase gene expression, which leads to increased cellular cholesterol biosynthesis and can possibly result in macrophage cholesterol accumulation and foam cell formation (6). Consistent with these findings, the functional responses of these cells to Ang II stimulation (*e.g.*, calcium release and cell proliferation) are also enhanced. The underlying mechanism for this upregulation of the AT1 receptor was found to be mRNA stabilization rather than alteration of the transcription rate (7, 8). These studies in cultured cells provided a mechanism that could link hypercholesterolemia to enhanced sensitivity of the vessel wall to Ang II stimulation. Interestingly, vascular superoxide production is also increased in hypercholesterolemia, and this is associated with a profound alteration of endothelium-dependent vasodilatation. These abnormalities are corrected by blockade of the AT1 receptor without accompanying effects on blood pressure or lipoprotein cholesterol levels. Furthermore, the Ang II infusion in hypercholesterolemic subjects resulted in a blood pressure increase that was more than double the increase observed in normocholesterolemic subjects, and expression

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of AT1 receptors was increased in hypercholesterolemic subjects (9). These findings strongly support the concept that hypercholesterolemia increases AT1 receptor expression and can contribute to atherosclerosis, and further suggest a molecular link between hyperlipidemia and hypertension (5, 10, 11).

Ang II indirectly facilitates this step by activating membrane-based NAD(P)H oxidase, which promotes the production of superoxide radicals (1–3). Oxidant stress triggered by Ang II may contribute to enhanced oxidation of LDL cholesterol and degradation of NO. The pluripotent peptide Ang II regulates the expression of oxidized LDL receptors biochemically distinct from the scavenger receptors, and this may contribute to endothelial dysfunction and accumulation of lipids in atherosclerotic plaques, as well as to later stages of atherosclerosis characterized by increased smooth muscle cell content, increased matrix deposition, and the accumulation of fibrinogen and fibrin in the plaque. Ang II is also a mitogen for vascular smooth muscle cells and stimulates the accumulation of the extracellular matrix *via* upregulation of transforming growth factor- β ; additionally, it can promote plasminogen activator inhibitor-1 synthesis in vascular tissue, which 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 (5).

A previous study showed that genetic disruption of the Ang II type 1a (AT1a) receptor leads to inhibition of vascular oxidative stress, endothelial dysfunction, and atherosclerotic lesion formation in apolipoprotein E (apoE)–knockout mice irrespective of blood pressure and plasma cholesterol levels, indicating a fundamental role of AT1 receptor activation in atherogenesis (12). Aging is also associated with activation of local tissue RAS and systemic RAS blockade prevents other age-related changes; this strongly suggests that mechanisms involving the blockade of local-tissue RAS contribute to the protective effects of systemic RAS blockade during aging (13). Importantly, other components of the local RAS in vessel walls such as angiotensin-converting enzyme (ACE) are also upregulated during atherosclerosis, and a high abundance of Ang II has been shown in atherosclerotic plaques as well as in hypercholesterolemia (3, 14, 15). Therefore, enhanced production of Ang II coincides with AT1 receptor upregulation, which may lead to increased efficacy of the RAS with subsequent deleterious consequences. Regulation of these factors is likely completely independent of the circulatory system, which appears to not be differentially regulated during atherosclerosis (3).

In this issue of *Hypertension Research*, Eto *et al.* describe the long-term effect of AT1a deficiency on hypercholesterolemia-induced atherosclerosis using AT1a-knockout mice and apoE-knockout mice (16). AT1a-knockout mice were crossed with apoE-knockout mice, generating double-knockout mice. The atherosclerotic lesions of the double-knockout mice were significantly smaller than those of apoE-knockout mice at 25 and 60 weeks of age. Surprisingly, there were no

significant differences in the atherosclerotic lesion size of double-knockout mice at 25 and 60 weeks, suggesting that AT1a deficiency completely protected against the age-related progression of atherosclerosis of apoE-knockout mice. Reduction of oxidative stress, apoptosis, and matrix metalloproteinase expression in atherosclerotic lesions by AT1a deficiency may have also contributed to the observed effect on plaque size. This inhibition of the development of vascular pathology was not attributable to a decrease in plasma cholesterol, indicating that interruption of the local RAS by AT1a deficiency halted the progression of atherosclerosis independent of blood pressure and plasma cholesterol level. These results are consistent with those of previous reports (17–19), suggesting that the AT1 receptor may provide a major contribution to the development and progression of atherosclerotic lesions independent of blood pressure and hypercholesterolemia. In addition, Eto *et al.* also showed that long-term inhibition of the AT1 receptor may be effective for preventing age-related progression of atherosclerosis (16).

Thus, AT1 receptor blockade may represent a novel approach for the prevention of vascular dysfunction and the progression of atherosclerosis associated with hypercholesterolemia independent of lipid- and blood pressure-lowering interventions (20), and inhibition of AT1 receptor activation may become a primary treatment goal for patients suffering from cardiovascular risk factors or manifesting atherosclerotic diseases (1, 5). Fujita *et al.* recently reported that although there were no statistically significant differences in event rates between patients receiving statins or RAS inhibitors and those receiving neither, Kaplan-Meier analysis of the event rate in combined treatment of statins with RAS inhibitors showed a 22% decrease in cardiovascular events in patients with coronary artery disease (21). In clinical settings, administration of RAS inhibitors at early stages of atherosclerosis followed by long-term use might be advised for treating progressive atherosclerosis and for preventing future cardiovascular events in patients with hypercholesterolemia.

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