EDITORIAL COMMENT

Multiple Actions of Angiotensin II in Hypertension: Benefits of AT1 Receptor Blockade*

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Hypertension, which is characterized by small artery disease (1), is also often associated with large artery disease, characterized at the level of large conduit arteries by arteriosclerosis (thickening and fibrosis of the media) and accentuated progression of atherosclerosis (2). Increasingly it has been appreciated that atherosclerosis has an inflammatory component that plays an integral role in its pathogenesis (3), and which is also present in other conditions associated with cardiovascular events such as hypertension (4) and diabetes mellitus (5). Indeed, inflammation is now recognized as a central mechanism contributing to progression of cardiovascular disease in general and may be involved particularly in the triggering of myocardial ischemia and infarction (6). Tissue expression and plasma concentration of inflammatory markers and mediators are increased in patients with cardiovascular disease (7). These markers and mediators of inflammation include C-reactive protein (CRP) (7), adhesion molecules such as vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) (7–10), chemokines such as monocyte chemotactic protein-1 (MCP-1), as well as anti-inflammatory agents such as plasminogen activator inhibitor-1 (PAI-1). Increased CRP has been shown to occur in hypertension (4); in experimental hypertension, upregulation of inflammatory mediators in tissues—such as nuclear factor kappa B (NF kappa B), activator protein-1 (AP-1), the adhesion molecules VCAM-1, ICAM-1, and platelet endothelial cell adhesion molecule, and tissue factor—have been demonstrated (11). In the presence of endothelial dysfunction that is often found in hypertensive patients—particularly if, as often is the case, obesity, dyslipidemia, insulin resistance, and other manifestations of the metabolic syndrome occur (12)—upregulation of adhesion molecules contributes to monocyte and macrophage invasion of the vascular wall, which in the setting of enhanced oxidative stress and generation of oxidized low-density lipoprotein cholesterol will participate

in the development and progression of the atherosclerotic plaque (13). Thus, endothelial dysfunction and oxidative stress have been recognized as markers or mediators leading to cardiovascular events (14). As inflammation is accentuated, activation of matrix metalloproteinases (MMPs) by different mechanisms triggers digestion of the fibrous cap, precipitating its rupture and triggering cardiovascular events (15).

Angiotensin II, via the type-1 (AT1) receptor, stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and enhances production of reactive oxygen species (ROS) (16), which in turn contributes to endothelial dysfunction by inactivating nitric oxide (17), and to vascular inflammation by stimulating NF kappa B and AP-1, and by upregulating adhesion molecules, cytokines, and chemokines (18). These events result in accelerated progression of atherosclerosis (19). As well, angiotensin II stimulates production of PAI-1 (20), which may contribute not only to the prothrombotic state but also to plaque rupture. In fact, mice in which the PAI-1 gene has been deleted are protected from the disseminated coronary artery fibrosis and thrombosis associated with Nω-nitro-l-arginine methyl ester (l-NNAME) treatment and nitric oxide synthase inhibition (21). Angiotensin II also stimulates activations of MMPs, which can digest the fibrous cap and thereby contribute to the pathophysiology of plaque rupture (15,22).

It follows from the previous evidence that blockade of the angiotensin AT1 receptor in hypertensive patients should result in reduced oxidative stress, inflammatory markers, fibrinolysis inhibition, and endothelial dysfunction. In this issue of the Journal, Koh et al. (23) demonstrate that hypertensive patients treated with an angiotensin receptor blocker (ARB) (candesartan) present improved endothelial function, diminished plasma concentration of a systemic marker of oxidative stress (thiobarbituric acid reactive substances [TBARs] measured as malonaldehyde in plasma), as well as tumor necrosis factor-alpha, MCP-1, and reduced PAI-1, but no decrease in CRP, MMP-9, or fibrinogen. There were no significant correlations of the decrease in inflammatory markers and reduction of systolic or diastolic blood pressure (BP), or with correction of endothelial dysfunction, which was measured by the hyperemic response of the brachial artery. This may suggest BP-independent effects of renin–angiotensin blockade in hypertension, as we previously proposed in the correction of small artery remodeling by these agents (24).

If reproducible in other cohorts of patients and with other similar antihypertensive agents, these findings may indicate an antiatherosclerotic effect of AT1 receptor blockers as concluded by Koh et al. (23). These data are therefore important, but some caveats and limitations need to be taken into account. This investigation took place over a limited period of two months. A recent study suggested that whereas angiotensin–converting enzyme inhibitors reduce PAI-1 over long periods of time, ARBs do so only tran-
siently (25). Thus, new and longer studies are necessary to ascertained that indeed ARBs will have these beneficial effects at least on PAI-1 with a more prolonged time-course than suggested by these other studies (25). In addition, it needs to be stressed that global markers of inflammation and oxidative stress were measured. Whether increased levels of these circulating markers do in fact reflect vascular inflammation and injury and whether reductions in plasma concentrations are associated with vascular repair and improved cardiovascular outcomes in hypertensive patients remains to be demonstrated. Be it as it may, the role of angiotensin II, initially thought to be limited to vasoconstriction, has by now been extended to actions on the heart, the brain, the kidney, and other organs, with a multiplicity of cardiovascular and noncardiovascular effects. With respect to cardiovascular actions, it has become evident that angiotensin II not only stimulates contraction but also enhances growth and extracellular matrix deposition—particularly of collagen and fibronectin—and stimulates apoptosis and the production of cytokines, adhesion molecules, PAI-1, and MCP-1, all probably to a large measure mediated by increased oxidative stress in the vascular wall (26). Indeed, Koh et al. (23) demonstrate a reduction in plasma TBARs in hypertensive patients treated with the ARB candesartan, suggesting decreased generation of ROS. Experimental and clinical evidence over the last few years has suggested that increased oxidative stress plays a pathophysiologic role in cardiovascular disease, including atherosclerosis, hypertension, and heart failure (27,28).

Superoxide anion and hydrogen peroxide are two of the ROS among others that function as signaling molecules regulating vascular tone and structure (29,30). In the vasculature, NAD(P)H oxidase appears to be the enzyme primarily responsible for generation of superoxide anion (27). The neutrophil/macrophage NAD(P)H oxidase contains five subunits: p40phox (phox for PHagocyte OXidase), p47phox, p67phox, p22phox, and gp91phox (31). p40phox, p47phox, and p67phox occur in the cytoplasm, whereas p22phox and gp91phox are found in the cell membrane as cytochrome b558. Subunits of the leukocyte NAD(P)H oxidase system are also present in non-phagocytic cells, including cells of the vasculature (16). Angiotensin AT1 receptor activates protein kinase C, phospholipase D, or Src (32,33) to stimulate NAD(P)H oxidase. These intermediate steps result in phosphorylation of p47phox, which in association with the other cytosolic subunits translocates to the membrane. Association with cytochrome b558 results in formation of active NAD(P)H oxidase (34). Two low-molecular-weight guanine nucleotide-binding proteins, Rac 2 (or Rac 1) and Rap1A also participate in the activation of NAD(P)H oxidase. All subunits of the neutrophil NAD(P)H oxidase are found in the three layers of the vascular wall (31,35), although the identity of the homologue of gp91phox detected in smooth muscle cells is controversial and may depend on the species and the vessel considered. In vascular smooth muscle cells derived from human resistance arteries, we recently demonstrated that gp91phox and nox4 (for NADPH Oxidase) are present, whereas nox1, which is found in rat vascular smooth muscle (32), is undetectable in human smooth muscle cells (36). Whether theTBARs detected in plasma in the study of Koh et al. (23) derive mostly from ROS generated in blood vessels, or whether there is a contribution of other organs is unclear. Whatever their origin, it is evident that candesartan by blocking AT1 receptors is able to reduce ROS generation, and thereby downregulate some of the proinflammatory, proatherosclerotic agents generated. This is supported by a recent publication which, using DNA microarray technology, identified genes stimulated in response to angiotensin II (37) and demonstrated upregulation of inflammatory mediators such as osteopontin, PAI-1, MCP-1, and tissue factor.

Together with previous data showing the proinflammatory effect of angiotensin II–induced ROS leading to NF kappa B and AP-1 upregulation (38–40), the present study accomplishes the task of translating to the bedside our knowledge of the pleiotropic actions of angiotensin II and using this information to understand some of the benefits that can be derived from blocking the pathophysiologic cardiovascular actions of angiotensin II on AT1 receptors to prevent complications of hypertension and progression of vascular disease in hypertensive patients.

REFERENCES


