Role of Endothelin-1 in Hypertension and Vascular Disease

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Endothelin-1 (ET-1) is a powerful vasoconstrictor peptide and regulator of blood flow that plays an important role in blood pressure (BP) elevation in some models of experimental hypertension such as DOCA-salt rat, DOCA-salt-treated spontaneously hypertensive rats (SHR), stroke-prone SHR, Dahl salt-sensitive rats, angiotensin II-infused rats, and one-kidney, one-clip Goldblatt rats, but not in SHR, two-kidney, one-clip hypertensive rats, transgenic (mREN2)27 rats, or Nω-nitro-L-arginine methyl ester chronically treated rats. In those models of hypertension in which ET-1 plays a vasoconstrictor role, ET-1 was shown to be overexpressed in the vessel walls, or BP has been lowered by administration of ET A/B- and ET A-selective receptor antagonists. In these experimental models, endothelin receptor antagonists also regressed vascular growth and inflammation, and improved endothelial dysfunction. Hypertensive rats treated with endothelin antagonists were protected from stroke and renal injury. In hypertensive rats without generalized vascular overproduction of ET-1, expression of ET-1 was often enhanced in intramyocardial coronary arteries, suggesting a role of ET in myocardial ischemia in hypertension. Moderate-to-severe hypertensive patients presented enhanced expression of proET-1 mRNA in the endothelium of subcutaneous resistance arteries, suggesting that this stage of hypertension may respond particularly well to endothelin antagonism. In some hypertensive patients, exaggerated vascular responses to ET-1 were found. Hypertensive patients with coronary artery disease have increased arterial expression of ET-1. Increased plasma levels of immunoreactive ET have been described in African Americans. ET-1 plays an important role in atherosclerosis, for which hypertension is an important risk factor, and in ischemic heart disease and stroke. Endothelin-1 may also be involved in other forms of vascular disease, including pulmonary hypertension, after angioplasty restenosis, after allograft vasculopathy, and vasculitis. Thus, ET-1 may participate in vascular damage in cardiovascular disease and in BP elevation in experimental models and in human hypertension. Endothelin antagonists could become effective disease-modifying agents in different forms of cardiovascular disease. Am J Hypertens 2001;14:83S–89S © 2001 American Journal of Hypertension, Ltd.

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receptors. Endothelin-1 is probably an important regulator of tissue blood flow through constrictor or dilator effects in different vascular beds.

In this review the role of endothelin will be discussed in hypertension and in atherosclerosis. The role of endothelin in other forms of cardiovascular disease, such as ischemic heart disease and myocardial infarction, stroke, restenosis after angioplasty, after allograft vasculopathy, pulmonary hypertension, or collagen vascular disease, will not be discussed and has been the subject of other reviews.

**Hypertension**

**Role of Endothelins in Experimental Hypertension**

Endothelin-1 production is enhanced in salt-sensitive hypertension. Several studies have reported that in DOCA-salt and aldosterone-salt hypertensive rats, DOCA-salt-treated spontaneously hypertensive rats (SHR), Dahl salt-sensitive rats, one-kidney, one-clip Goldblatt hypertensive rats, and stroke-prone SHR there is overexpression of preproET-1 mRNA in the endothelium and BP lowering upon administration of endothelin antagonists. In SHR, DOCA-salt hypertensive rats do not seem to play an important role, although increased vasoconstrictor response to ET-1 has occasionally been reported in SHR. Hyper trophy remodeling of resistance arteries has been a characteristic finding in most models in which ET-1 was shown to lower BP, and these vascular changes regressed upon administration of endothelin antagonists. The growth-promoting action attributed to ET-1 involves not only a hypertrophic and hyperplastic effect, but also a survival role of ET-1 on vascular smooth muscle cells. Blockade of ET-1 action with receptor blockers was associated with increased rate of apoptosis (programmed cell death) in the tunica media of the arterial wall. Endothelin-1 is produced in the kidney in the endothelium of vessels and in tubules, and its production is enhanced in blood vessels and glomeruli in DOCA-salt hypertensive rats, leading to renal vasoconstriction and water and sodium retention. DOCA-salt-treated SHR develop malignant hypertension and vascular and glomerular fibrinoid necrosis, and endothelin antagonists reduce renal vascular and glomerular injury.

Mechanisms leading to the participation of ET-1 in experimental hypertension are unclear. Angiotensin II-infused rats overexpress preproET-1 and endothelin antagonists reduce BP and regress vascular remodeling, which suggests that ET-1 mediates the effects of angiotensin II. In contrast, endothelin antagonists do not lower BP in renin-dependent two-kidney, one-clip Goldblatt hypertensive rats, or in transgenic (mREN2)27 rats. Spon taneously hypertensive rats and the chronic NO-nitro-L-arginine methyl ester (L-NAME)-treated rat do not respond to endothelin antagonists with BP lowering, although they do respond to angiotensin antagonism. It is unclear at present why exogenous angiotensin II-infused rats have an endothelin-dependent component, endogenous angiotensin, renin-dependent models do not, and low-renin, salt-dependent models typically have an activated endothelin system that contributes to BP elevation and vascular damage. Recently, the model of transgenic expression of human renin and angiotensinogen in rats, which develop rapidly malignant and fulminating hypertension, was shown to present severe inflammatory vascular and renal changes that may be abrogated by endothelin antagonist treatment. Thus, when hypertension is severe, in low renin or in some forms of high angiotensin hypertension, ET-1 production is enhanced and contributes to vascular damage and the severity of BP elevation and its complications. Other peptides and agents may participate as well in stimulation of vascular production of ET-1 leading to vascular damage in hypertension. In DOCA-salt hypertensive rats that have an endothelin-dependent component, plasma vasopressin is increased and its effects enhanced. A V1-vasopressin antagonist abrogated the enhanced vascular preproET-1 gene expression in DOCA-salt hypertensive rats, lowered BP, and regressed vascular hypertrophy. Vasopressin-deficient Brattleboro rats did not develop hypertension with DOCA-salt treatment, in part because they were unable to upregulate preproET-1 gene expression. Thus, vasopressin, which stimulates production of ET-1 by the endothelium, may participate in stimulation of preproET-1 gene expression in this model. Whether vasopressin is involved in other hypertensive models has not been studied. We recently demonstrated that in aldosterone-infused rats, vascular preproET-1 gene expression is increased, and BP may be lowered and vascular hypertrophy regress upon treatment with an ET(A) antagonist.

Those forms of experimental hypertension that respond to endothelin antagonism typically present severe hypertension of small arteries. These effects are mediated in part by the mitogenic and cell hypertrophic actions of ET-1 on smooth muscle, and endothelin antagonist treatment is able to regress hypertrophic remodeling of small arteries despite exerting only moderate BP-lowering action, suggesting a direct effect of ET-1 on blood vessel growth. In stroke-prone SHR, endothelin antagonist treatment induces a regression of vascular damage and improvement of endothelial dysfunction, and this is associated with reduction in stroke and dramatic prolongation of lifespan. Recent studies have elucidated some of the mechanisms involved in the vascular damage induced by endothelin, and these include increased oxidative stress, leading to activation of redox-sensitive genes, stimulation of NF kappaB and activator protein S-1 (AP-1), upregulation of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), monocyte chemotactic peptide-1 (MCP-1), and other mediators leading to attraction of macrophages and neutrophils into the vascular wall, which, together with stimulation of growth factor induction, results in the growth and inflammatory response.
found in some of the models in which ET-1 has been implicated (Fig. 1).

Smaller vessels may also participate in changes induced by ET-1 in experimental hypertension. Arteriolar density in the subendocardial myocardium of the left ventricle of DOCA-salt hypertensive rats was increased, suggesting a growth response, and capillary rarefaction occurred, contributing to myocardial damage as oxygen/nutrient exchange is compromised. These findings are prevented by treatment with an ET A receptor antagonist. The endothelium of coronary arteries presents an increased message for ET-1 in several forms of hypertension because it may be particularly vulnerable to the effects of elevated BP. In two-kidney, one-clip hypertensive rats or in the L-NAME-treated rat that becomes hypertensive due to nitric oxide deficiency, increased preproET-1 mRNA is found in the coronary endothelium. Thus, in hypertension ET-1 may have a significant role in myocardial ischemia. Periconorary fibrosis may be improved by treatment with the ET A/ET B receptor antagonist bosentan in SHR, although this model of genetic hypertension does not possess a significant endothelin-dependent component. In other models, such as DOCA-salt hypertensive rats or after infusion of aldosterone in salt-loaded rats (J.B. Park and E.L. Schiffrin, unpublished observations, 2000), significant perivascular and interstitial fibrosis of the heart occurs, which is mediated by overexpression of preproET-1 and TGF-β.

**The Vascular Endothelin System in Human Hypertension**

Although endothelin plasma levels are high in severely hypertensive patients and hypertensive African Americans, they are usually normal in human hypertension. In African Americans we have recently found that plasma endothelin may not be higher than in Caucasians if patients with similar severity of hypertension are compared. An endothelin-dependent vascular tone has been demonstrated in healthy subjects by the response to acute intravenous administration of TAK-044, a mixed ET A/ET B endothelin receptor antagonist that induced an increase in forearm blood flow and slightly lowered BP. In a recent study by Cardillo et al., an increased vasoconstrictor responsiveness of forearm blood flow was demonstrated in hypertensive patients. This contrasts with reduced responsiveness we had found some years ago in vitro in vessels obtained from glutel subcutaneous biop-

**FIG. 1.** Diagram represents some of the actions of endothelin-1 (ET-1) that mediate its effects in hypertension and contribute to vascular damage. ET-1 production is stimulated by elevated pressure, angiotensin II, vasopressin, LDL cholesterol, and other stimuli, and predominantly through activation of ET A receptors, it stimulates vasoconstriction, growth of smooth muscle cells, and their migration. Production of growth factors (TGF-β) is enhanced, leading to fibrosis. Inflammatory mediators are stimulated, including NF-κB and AP-1, in part through stimulation of production of superoxide anion and the action of oxidized LDL-cholesterol (ox-LDL), contributing to vascular damage. These effects are associated with upregulation of adhesion molecules (VCAM-1, ICAM-1) and chemokines like MCP-1, cytokines such as TNF-α and interleukins, resulting in attraction of macrophages, stimulation of production of foam cells, inflammation, and atherogenesis.
Atherosclerosis

Atherosclerosis involves injury of endothelial cells, inflammation with macrophage and monocyte infiltration of the vessel wall, release of cytokines and growth factors, migration of smooth muscle cells to the intima, and lipid accumulation in foam cells. Evidence has recently accrued suggesting involvement of ET-1 in these processes leading to atherosclerosis development and progression. Endothelin-1 is chemotactic for monocytes and macrophages and acts as a comitogen for vascular smooth muscle cells together with growth factors. Plasma endothelin is elevated in subjects with risk factors for atherosclerosis such as hyperlipidemia and cigarette smoking, and patients with coronary endothelial dysfunction and early atherosclerosis. Plasma and tissue endothelin are elevated in proportion to the extension of atherosclerosis in patients with advanced disease. Smooth muscle and macrophages in coronary plaques from patients with unstable angina have greater endothelin immunoreactivity than patients with stable angina. Endothelin-1 immunoreactivity was localized in endothelium and adventitia, and regions of neovascularization and recanalization in atherosclerotic plaques from human coronary arteries. Significant endothelin-converting enzyme-1 (ECE) immunoreactivity was present in smooth muscle and macrophages in human coronary atherosclerotic lesions. Active ECE-1-α and -β have been reported in cholesterol-fed New Zealand rabbits with increased ET-1 formation and progression of atheroma. ET<sub>B</sub> receptors are upregulated in atherosclerotic human coronary arteries. However, no change in ET<sub>A</sub> and ET<sub>B</sub> proportions in the media of coronary arteries was detected by other investigators. Interestingly, Rossi et al showed that hypertensive and atherosclerotic individuals exhibited increased immunoreactive endothelin in the media of internal mammary arteries.

Many components of human atherosclerotic lesions such as endothelial cells, macrophages, and smooth muscle cells express ET-1. Neovascularization is an important component of the atherosclerotic plaque, and ET<sub>B</sub> receptors on endothelial cells of neovessels may imply an angiogenic role of ET-1 in atherosclerosis contributing to plaque formation. Oxidized LDL induced ET-1 production by the endothelium. Blockade of the ET<sub>A</sub> receptors decreased atherosclerosis in apoE knockout mice and in hamsters fed a high cholesterol diet. Mechanisms whereby increased ET-1 may contribute to atherosclerosis include stimulation of migration of smooth muscle cells into the intima of vessels, activation of inflammation in the vessel wall by stimulating cytokines such as interleukin-6 and proinflammatory molecules like NF-κB, or chemokines like MCP-1 and by increasing oxidative stress.

Conclusion

Endothelin-1 appears to play important roles in hypertension and different forms of vascular disease (Fig. 1). It plays a role in BP elevation and vascular growth in moderate-to-severe hypertension, in salt-sensitive forms of hypertension, and perhaps in special populations such as African Americans. Endothelial damage may activate expression of ET-1 in vessels and in the heart as BP increases. Endothelin then contributes to both BP elevation and to progression of vascular damage and atherosclerosis. We believe that blocking the endothelin system may provide a new therapeutic approach beyond BP lowering in hypertension, contributing to arrest of vascular damage, and, accordingly, improve prognosis. This has been shown in experimental animals, but remains to be proven in humans with cardiovascular disease.

References


ET-1 IN HYPERTENSION AND VASCULAR DISEASE


