Angiotensin II Stimulates Proliferation of Human Pulmonary Artery Smooth Muscle Cells via the AT1 Receptor*

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(CHEST 1998; 114:905S-915S)

Inhibition of angiotensin-converting enzyme (ACE), or the angiotensin II (ANG II) type 1 receptor (AT1), is known to attenuate hypoxia-induced pulmonary hypertension in the rat. Furthermore, increased local expression of ACE has been reported in remodeled hypertensive pulmonary arteriolar smooth muscle cells of the hypoxic rat and patients with primary pulmonary hypertension, which has led to the hypothesis that increased local generation of ANG II by ACE mediates some of the structural changes in the remodeled pulmonary artery. We therefore questioned whether human pulmonary artery smooth muscle cells (SMCs) express functional ANG II receptors coupled to mitogenesis.

METHODS

SMCs were explant-derived from samples of lobar pulmonary artery obtained from patients undergoing lung resection and donors for heart-lung transplantation (n=4). Cell phenotype was confirmed immunohistochemically with antibodies to mesenchymal and endothelial cell antigens. Early passage cells (three to four) were used for studies of proliferation by cell counting and uptake of 3H-thymidine under serum-deprived conditions, with or without the addition of 10^{-6} M ANG II for 24 and 48 h. ANG II receptors were identified by binding with [125I](Sar^{Ile^{8}})ANG II (0.1 nM, 90 min, 37°C) to subconfluent cells. AT1 and AT2 receptor subtypes were distinguished by incubating cells with nonpeptide AT1 (losartan 10^{-6} M) or AT2 (10^{-6} M PD123319) antagonists.

RESULTS

The addition of 10^{-6} M ANG II to serum-deprived SMCs led to a marked stimulation of 3H-thymidine incorporation at 24 h (133% over control) and 48 h (183% over control) (p<0.01). Increase in cell number was apparent by 3 days. Specific [125I](Sar^{Ile^{8}})ANG II binding was demonstrated to all SMC lines and was inhibited by losartan but not by PD123319.

CONCLUSION

ANG II is mitogenic to human pulmonary artery SMCs, a response mediated by the AT1 receptor subtype. These findings support the hypothesis that ANG II contributes to the fetal pattern of tropoelastin gene expression in severe neonatal bovine pulmonary hypertension. J Clin Invest 1994; 93:1324-42


33 Botney MD, Bahadori L, Gold L. Vascular remodeling in primary pulmonary hypertension. Am J Pathol 1994; 144: 286-95


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Vascular Remodeling—The Emerging Paradigm of Programmed Cell Death (Apoptosis)*

The Francis B. Parker Lectureship

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(CHEST 1998; 114:91S-99S)

Vascular remodeling involves structural alteration of the blood vessel that occurs usually as an adaptive process in response to long-term changes in hemodynamic condition, but it may subsequently contribute to the pathophysiology of vascular disease and circulatory disorders. The remodeling process involves changes in one or more of the following events—cell growth, cell death, cell migration, and production or degradation of extracellular matrix—and is dependent on a dynamic interaction among locally generated growth factors, vasoactive substances, and hemodynamic stimuli.

SPECTRUM OF VASCULAR REMODELING

Table 1 summarizes the spectrum of vascular remodeling and Table 2 shows the clinical conditions involving vascular remodeling.1,2 A form of vascular remodeling involves changes primarily in luminal dimensions. In this example, active restructuring of the cellular and nonecellular components of the vessel wall results in marked changes in luminal dimensions, with relatively small changes in wall thickness. Clinical examples of this form of remodeling include the vascular dilations associated with sustained high blood flow (eg, an arteriovenous fistula) or the cell loss and matrix proteolysis that results in aneurysm formation. Conversely, a reduction of the vascular mass and caliber results from a long-term reduction in blood flow. Indeed, rarefaction of the microcirculation (a loss of capillary area) is another form of vascular remodeling that promotes hypertension and tissue ischemia.3 In response to increased arterial pressure, the vessel structure is altered such that the ratio of the width of the wall to the width of the lumen is elevated by either an increase in muscle mass or rearrangements of cellular and nonecellular elements. These changes heighten vascular reactivity, which potentiates the increase in peripheral resistance characteristic of hypertension.4-6 The architecture of the vessel wall is also markedly altered in response to vascular injury. A neointima forms as part of a reparative response to injury that involves thrombosis, migration, proliferation of vascular cells, matrix production, and inflammatory cell infiltration.

*A Novel Orally Active Endothelin-A Receptor Antagonist, ZD1611, Prevents Chronic Hypoxia-Induced Pulmonary Hypertension in the Rat*

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Endothelin-1 (ET-1) is a potent vasoconstrictor peptide with comitogenic properties isolated originally from the conditioned media of vascular endothelial cells. Recently, ET-1 has been implicated in the pathogenesis of pulmonary hypertension (PH). Studies were undertaken to evaluate the effect of the novel ETA receptor-selective antagonist ZD1611 on the development of hypoxia-induced PH in rats. A prophylactic paradigm was established in which placebo or ZD1611 (3 mg/kg, qid, po) were administered to male Sprague-Dawley rats concomitant with hypoxic exposure (10% O2, 1 atm) for 14 days. In comparison with normoxic controls, hypoxic exposure of rats administered placebo caused a twofold increase (p<0.05) in the mass ratio of right ventricle over left ventricle plus septum. This effect was decreased (p<0.05) by ZD1611 (normoxia/placebo/ZD1611 = 0.22±0.02:0.42±0.01:0.36±0.01, n=9). After hypoxic exposure, mean right ventricle systolic pressure and mean systemic arterial pressure (MSAP) were measured over a 60-min period while rats respired room air. As compared with placebo controls, administration of ZD1611 caused a 32% decrease (p<0.05) in right ventricle systolic pressure (placebo/ZD1611 = 71±4:48±5 mm Hg, n=9). Hypoxic exposure did not alter MSAP, and MSAP was not affected by ZD1611. In separate studies, hypoxic exposure of placebo control rats decreased (p<0.05) both the sensitivity and maximum contraction to ET-1 in isolated extralobar left branch pulmonary artery and these changes were abolished by ZD1611 (sensitivity, placebo: ZD1611 = 8.98±0.10:9.42±0.11; % max, placebo/ZD1611 = 65±4:100±1; n=6). In conclusion, these data support the hypothesis that ET-1, acting on pulmonary vascular ETA receptors, plays a major role in the pathogenesis of chronic hypoxia-induced PH. ZD1611 may, therefore, be useful for the treatment of PH.

*From Cardiovascular Research, Department of Medicine, Harvard Medical School, Brigham and Women’s Hospital, Boston. This work was supported by NIH grants HL46531, HL35252, HL35610, HL46639, HL07708, by a grant from Bristol Myers Squibb, by the Fred and Edna Mandel Research Fund, and the Longwood Foundation for Translational Research. Dr. Dzau is recipient of NIH MERIT Award HL35610.