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VASCULAR DISEASE

INHIBITION OF THE ANGIOTENSIN II TYPE-1 (AT-1) RECEPTOR BY THE ANGIOTENSIN RECEPTOR BLOCKER AZILSARTAN MEDOXOMIL (TAK-491) SUPPRESSES AORTIC EXPRESSION OF PLASMINOGEN ACTIVATOR INHIBITOR TYPE-I (PAI-1) PROTEIN IN TRANSGENIC MICE OVEREXPRESSING PAI-1 IN VASCULAR SMOOTH MUSCLE CELLS

ACC Poster Contributions
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Introduction: Increased expression of PAI-1 in vessel walls has been implicated in accelerating atherogenesis and as a cardiovascular risk factor in patients with type 2 diabetes and the metabolic syndrome. Angiotensin II is known to increase synthesis of PAI-1 protein in diverse tissues.

Methods: To determine whether long-term inhibition of the angiotensisn II type-I (AT-1) receptor blunts overexpression of PAI-1 protein in the aortic wall despite upregulation of the PAI-1 gene in VSMCs we administered azilsartan medoxomil (AZL-M), a prodrug of an AT-1 receptor blocker developed by the Takeda Pharmaceutical company, to ApoE knockout mice on a C57BL6 background rendered overexpressors of PAI-1 in vessel walls by insertion of a PAI-1-SM22 alpha promoter transgene. AZL-M in peanut butter (long-term stability verified by HPLC) in doses of 0.1, 1, or 10 mg/kg body weight or vehicle alone (controls) was administered daily for 16 weeks to mice on a high fat diet (8 per group) beginning at 4 weeks of age. Descending aortas were harvested 16 weeks later. Aortic homogenates from each group were pooled to provide adequate amounts of tissue and assayed for PAI-1 (ng/mg soluble protein) by ELISA and total soluble protein by the Bradford procedure.

Results: Serially obtained blood pressures were virtually identical in all groups and remained normal throughout the study. Pooled aortic wall PAI-1 from 4 C57BL6 mice without the transgene averaged 3.0 ng/mg soluble protein. Aortic PAI-1 was markedly higher in the 8 control transgenic mice, averaging 10.9 ng/mg. The increase was attenuated by each of the 3 dosage regimens of AZL-M averaging 9.6, 4.1, and 5.2 ng/mg with 0.1, 1 or 10 mg/kg, respectively (8 aortas in each pool).

Conclusion: AZL-M suppresses overexpression of PAI-1 in aortas of transgenic mice overexpressing PAI-1. These results indicate that activation of the AT-1 receptor is necessary for full expression of PAI-1 protein despite augmentation of synthesis driven by upregulation of the PAI-1 gene in vessel walls. Accordingly, AZL-M suppression of PAI-1 expression may be useful in attenuating untoward effects on the evolution of atherosclerotic plaques driven by PAI-I rendering them vulnerable to rupture.