Pulmonary hypertension

Endothelial pathways mediating the prevention of pulmonary hypertension by atrial natriuretic peptide

*F. Werner[1], B. Kojonazarov[2,3], B. Gaßner[1], M. Abeßer[1], K. Schuh[1], K. Völker[1], H. A. Baba[4], B. K. Dahal[2,3], R. T. Schermuly[2,3], M. Kuhn[1]
[1]University of Würzburg, Institute of Physiology I (Würzburg, Germany)
[2]University of Giessen and Marburg Lung Center (UGMLC), Justus-Liebig University Gießen, Department of Internal Medicine (Gießen, Germany)
[3]German Center for Lung Research (Gießen, Germany)
[4]University Hospital of Essen, University of Duisburg-Essen, Institute of Pathology (Essen, Germany)

Atrial natriuretic peptide (ANP) activates the cyclic GMP-producing cyclase-A (GC-A) receptor and regulates systemic/pulmonary arterial blood pressure. Mechanisms of maintenance of pulmonary blood pressure homeostasis by ANP are largely unknown. Our aim was to investigate GC-A/cGMP signalling in lung EC and the cause/impact of its dysfunction. Pulmonary EC showed strong GC-A expression and ANP-induced activity (increased cGMP content, cGMP-dependent protein kinase I (cGKI)-induced VASP phosphorylation). *In vitro*, stressors involved in pulmonary hypertension (PH), like hypoxia or tumor necrosis factor α, markedly blunted endothelial GC-A expression/function. Concomitantly, exposing mice to hypoxia (10% oxygen, 3 weeks) downregulated pulmonary GC-A expression and ANP-responsiveness. To dissect the significance of endothelial GC-A dysfunction for lung vascular (patho)physiology we studied mice with endothelial-specific ablation of this receptor (EC GC-A KO mice). Under normoxic conditions these mice showed increased pulmonary mRNA expression of endothelial pro-inflammatory adhesion molecules (ICAM-1, VCAM-1 and E-selectin) and angiotensin converting enzyme, resulting in increased local Angiotensin II concentrations. Changes were accompanied by subtle but significant pulmonary vascular remodelling, perivascular inflammatory infiltration and PH and were exacerbated under hypoxic conditions. Treatment with losartan, an Angiotensin II/AT1-antagonist, reversed pulmonary remodelling and perivascular inflammation of EC GC-A KO mice, and prevented worsening after hypoxia. These alterations were not observed in mice with global VASP or endothelial-restricted cGKI ablation, indicating that these proteins do not mediate the protective endothelial actions of ANP/GC-A signalling. In conclusion, ANP prevents endothelium-dependently pulmonary vascular remodelling and PH. Chronic dysfunction of the ANP/GC-A system activates proinflammatory EC signalling and thereby vascular remodelling.