Hypoxia-Induced Changes in the Murine Pulmonary Circulation are Attenuated by Treatment with sRAGE

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Rationale

The receptor for advanced glycation end-products (RAGE) is a 45 kDa protein of the immunoglobulin super-family that has been recently implicated in the pathogenesis of pulmonary hypertension; a progressive disease of the small pulmonary arteries characterised by vascular remodeling and narrowing, increased pulmonary vascular resistance and a sustained increase in pulmonary pressure. Activation of RAGE by the RAGE ligand S100A4/MTS1, which is exocytosed by pulmonary endothelial and smooth muscle cells, appears to be key to the proliferatory and migratory responses of these cells to stimuli such as 5-Hydroxytriptamine (5-HT). RAGE may therefore have a role in the remodelling of pulmonary vessels and the pathogenesis pulmonary hypertension.

Methods

Male C57/BL6 mice aged 12-16 weeks were randomly assigned to either normoxia or hypoxia and were treated I.P. with either 20μg/day of the soluble form of RAGE (sRAGE) or 20μg/day murine serum albumin (MSA). Mice in the hypoxic group were placed in a hypobaric chamber and the pressure was reduced to 550mbar for a period of two weeks. At the end of this period, mice were removed from the chamber, anaesthetised and right ventricular pressure was assessed in vivo. After euthanasia, heart and lungs of each animal were excised and used to assess right ventricular hypertrophy (RVH). Statistical analysis was by two-way analysis of variance.

Results

Exposure to two weeks hypoxia resulted in an elevation in RVP, RVH and remodelling in animals treated with vehicle. Treatment with sRAGE prevented the increase in RVP but not in RVH.

Discussion

That treatment with sRAGE prevented hypoxia-induced increases in RVP provides further evidence of a role for RAGE and its ligands in the hypoxia induced pulmonary hypertension.