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Poster presentation

Activation of soluble guanylate cyclase reverses pulmonary vascular remodeling induced by hypoxia in mice

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Background

Chronic hypoxia is one of the major causes of pulmonary vascular remodeling associated with right heart hypertrophy. Recent studies have indicated that hypoxia upregulates expression of the soluble guanylate cyclase (sGC), which is activated by the vasodilator nitric oxide (NO). Thus, using wild type and homozygous endothelial nitric oxide synthase (NOS3$^{-/-}$)-knockout mice, we examined whether activation of sGC by BAY 41-2272 or BAY 58-2667 could reverse pulmonary vascular remodeling induced by hypoxia in mice.

Methods and Results

Ten-week-old male wild-type (NOS3$^{+/+}$) or NOS3$^{-/-}$ mice were housed under 10% oxygen conditions for 21 or 35 days. In NOS3$^{+/+}$ mice, hypoxia induced pulmonary hypertension and pulmonary vascular remodeling, demonstrated by an increase in fully muscularized peripheral pulmonary arteries. Treatment of mice with the activators of the sGC, BAY 58-2667 (10 mg/kg d) or BAY 41-2272 (10 mg/kg d), after full establishment of pulmonary hypertension from day 21 to day 35, reduced right ventricular (RV) systolic pressures (RVSPs), RV weight and vascular remodeling. In addition, both drugs inhibited the pressor response to acute hypoxia in the isolated perfused lung system. In NOS3$^{-/-}$ mice, only BAY 58-2667 reduced RVSP while both drugs did not reduce RV weight but significantly reversed muscularization of peripheral pulmonary arteries.

Conclusions

The present results suggest that activation of sGC reverses hypoxia-induced pulmonary hypertension and that the effects on right heart hypertrophy are dependant on endogenous nitric oxide from endothelial NOS.