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Poster presentation

Selective modulation of ANP-dependent dilatation in the pulmonary vasculature by PDE 5 inhibitors: a novel combination therapy for pulmonary hypertension?

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Background

Pulmonary hypertension has a high mortality, in part because of the paucity of selective pulmonary vasodilators. We have demonstrated previously that the phosphodiesterase (PDE) 5 inhibitor sildenafil augments dilatation to atrial natriuretic peptide (ANP) in the pulmonary, but not systemic, vasculature. This supports the hypothesis that cGMP-mediated vasodilatation by ANP is regulated by PDE V specifically in the pulmonary vascular bed, and that modulation of the natriuretic peptide system could be beneficial in the treatment of pulmonary hypertension.

Materials and methods

Male Sprague Dawley rats were divided into groups, pretreated with either ecadotril (neutral endopeptidase [NEP]inhibitor; prevents natriuretic peptide hydrolysis) 60 mg/kg/day by gavage, sildenafil 30 mg/kg/day in the drinking water, or a combination of both, and subjected to 2 weeks of hypoxia (10% oxygen) to induce pulmonary hypertension. Hypoxic and normoxic controls were also included. After two weeks, pulmonary, right ventricular and systemic pressures were determined by fluid filled catheterisation in anaesthetised animals. Animals were then euthanised and hearts and lungs excised for further analysis.

Results

In untreated control rats, 2 weeks of 10% hypoxia produced markedly elevated mean pulmonary pressures (28.9 ± 2.2 mmHg) as compared to normoxia controls (18.44 ± 1.9 mmHg; $P < 0.05$). Both sildenafil treated (24.07 ± 0.5 mmHg) and ecadotril treated (25.45 ± 1.4 mmHg) animals showed a statistically significant reduction in PAP with a further reduction (21.27 ± 1.4 mmHg) observed in the combined treatment group. Similarly, 2 weeks of hypoxia produced a doubling of the right ventricular systolic pressure (RVSP) in untreated hypoxic rats (41.2 ± 2.0 mmHg) as compared to normoxia controls (26.8 ± 6.6 mmHg; $P < 0.05$). Treatment with sildenafil (40.2 ± 4.5 mmHg) or ecadotril (41.3 ± 4.5 mmHg) alone failed to reduce RVSP, but the sildenafil + ecadotril group showed reduced RVSP (35.3 ± 1.8 mmHg; $P < 0.05$). Systemic blood pressure was not changed in any of the groups. In accord with the changes in pulmonary haemodynamics, the right ventricular hypertrophy (right to left ventricle weight ratio) and vascular remodelling in the lung (% of muscularised vessels) following hypoxia were reduced with each of the treatment regimes.

Conclusion

These data suggest that a combination of sildenafil and ecadotril has a synergistic effect to lower pulmonary arte-

rial pressure in pulmonary hypertension. However, there is no effect of this combination on systemic blood pressure, so the presence of NEP blockade appears to increases the pulmonary selectivity of sildenafil, and this combination treatment might be of therapeutic benefit in treating pulmonary hypertension.