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Poster presentation

Reperfusion lung injury is attenuated by natriuretic peptide receptor antagonist in *in-vivo* mouse model

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Background

Atrial natriuretic peptide (ANP) is released into the circulation by right atrial stretch and increases systemic vascular permeability through activation of natriuretic peptide receptor A (NPR-A) and generation of cGMP by particulate guanylate cylase.

Materials and methods

The NPR-A antagonist anantin was utilized in an in vivo mouse model of unilateral left lung IR (30 min:150 min), and pulmonary vascular permeability was assessed by Evans blue dye (EBD)-labeled albumin escape. The NPR-A signalling cascade was assessed by measurements of circulating and lung tissue levels of ANP, cGMP and phosphorylation of lung vasodilator-stimulated phosphoprotein (VASP). Additionally the effect of exogenous ANP administration on capillary filtration coefficient was determined in an in situ isolated perfused mouse model of lung IR.

Results

In spontaneously breathing mice, left lung IR increased EBD protein extravasation in the reperfused left lung compared to the unmanipulated right lung (left lung/right lung EBD = 2.3 ± 0.08; RL = 0.06 ± 0.00 AU, n = 8). Anantin attenuated this (left lung/right lung EBD = 1.69 ± 0.03, RL = 0.06 ± 0.00 AU, n = 8). Compared to control mice (n = 7), left pulmonary artery occlusion resulted in: a) a 10-fold increase ($P < 0.05$) in circulating ANP levels at 0 and 15 min of reperfusion; b) a 2-fold increase ($P < 0.01$) in left lung tissue cGMP content at 60 min of reperfusion (n = 6–7); c) no change in circulating or right lung cGMP concentrations; d) increased lung tissue expression of VASP phosphorylated at ser235 (the PKGI-preferred site) at 150 min of reperfusion ($P < 0.05$); e) no change in ser153 phosphorylation (the PKA-preferred site). Anantin treatment: a) further elevated circulating ANP levels; b) blocked the increase in tissue cGMP levels in the left lung; c) significantly decreased circulating cGMP at 60 min and ser235 VASP phosphorylation at 150 min (n = 4–12); d) had no effect on circulating or lung tissue cAMP. In the *in situ* lung IR preparation (30 min:60 min), ANP administration with reperfusion (2.5 nM) significantly increased capillary filtration coefficient (Kf) compared to diluent (4.3 ± 2.1 vs. 2.2 ± 0.7 g/min/mmHg/100 g WW; n = 5–7).

Conclusion

These data suggest that NPR-A stimulation by ANP contributes to pulmonary vascular injury following lung IR.