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Atrial natriuretic peptide improves *Staphylococcus aureus*-induced lung inflammation and vascular barrier function

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Lung inflammation and alterations in endothelial cell (EC) permeability are key events to development of acute lung injury (ALI). Protective effects of atrial natriuretic peptide (ANP) have been shown against inflammatory signaling and endothelial barrier dysfunction induced by gram negative bacterial wall liposacharide LPS. We hypothesized that ANP may possess more general protective effects and attenuate lung inflammation and EC barrier dysfunction by suppressing inflammatory cascades and barrier disruptive mechanisms shared by gram-negative and gram-positive pathogens. C57BL/6J wild type or ANP knockout mice (Nppa-/-) were treated with gram-positive bacterial cell wall compounds, Staphylococcus aureus-derived peptidoglycan (PepG) and/or lipoteichoic acid (LTA) (i/t, 2.5 mg/kg each), with or without ANP (i/v, 2 μg/kg). In vitro, human pulmonary EC barrier properties were assessed by morphological analysis of gap formation and measurements of transendothelial electrical resistance. LTA and PepG markedly increased pulmonary EC permeability and activated p38 and Erk-1, 2 MAP kinases, NFκB, and Rho/Rho kinase signaling. EC barrier dysfunction was further elevated upon combined LTA and PepG treatment, but abolished by ANP pretreatment. In vivo, LTA and PepG-induced accumulation of protein and cells in the bronchoalveolar lavage fluid, tissue neutrophil infiltration, and increased Evans blue extravasation in the lungs were significantly attenuated by intravenous injection of ANP. Accumulation of BAL markers of LTA/PepG-induced lung inflammation and barrier dysfunction was further augmented in ANP-/- mice and attenuated by exogenous ANP injection. These results strongly suggest a protective role of ANP in the in vitro and in vivo models of ALI associated with gram positive infection. Thus, ANP may have important implications in therapeutic strategies aimed at the treatment of sepsis and ALI-induced gram positive bacterial pathogens.

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