An Estrogen Receptor α (ERα)-BMPR2-Apelin Axis Mediates 17β-Estradiol (E2)'s Protective Effects On Right Ventricular (RV) Function in Experimental Pulmonary Hypertension (PH)

Andrea Frump1, Marjorie Albrecht1, Sandra Breuils-Bonnet2, Bakhtiyor Yakubov1, Mary Beth Brown1, Steeve Provencher2, Sebastien Bonnet2, Tim Lahm1,3

1Indiana University School of Medicine - Indianapolis, IN/US, 2University of Laval – Quebec City, Quebec/CA, 3Richard L. Roudebush VA Medical Center – Indianapolis, IN/US

Introduction: Women with pulmonary arterial hypertension (PAH) exhibit superior RV function and survival compared to men, a phenomenon attributed to poorly understood cardioprotective effects of E2.

Hypothesis: E2, through ERα, attenuates PH-induced RV dysfunction by up-regulating the pro-contractile and pro-angiogenic peptide apelin via a bone morphogenetic protein receptor 2 (BMPR2)-dependent mechanism.

Methods: ERα, BMPR2 and apelin were measured (western blot, RT-PCR) in RVs from PAH patients with compensated or decompensated RV hypertrophy (CRVH or DRVH) and in RV homogenates from male or female Sprague-Dawley rats with sugen/hypoxia (SuHx)-induced PH. H9c2 rat cardiomyoblasts were stressed with TNF-α (10 ng/ml) or staurosporine (50 nM) ± E2 (100 nM; 24 hrs). ERα-, BMPR2- and apelin-dependence were evaluated by siRNA (5 pM). Apelin downstream signaling was assessed by measurement of ERK1/2 activation. ERα binding to the BMPR2 promoter was assessed by ChIP. p<0.05 by ANOVA was considered significant.

Results: ERα correlated with BMPR2 and apelin expression in SuHx-RVs and human RVs. Treatment of SuHx-PH rats with E2 or ERα agonist increased RV BMPR2 and apelin, whereas RV apelin was decreased in E2-treated hypoxic ERα (p<0.05), but not ERβ knockout mice. In H9c2 cells, E2 or ERα agonist attenuated TNF-α- or staurosporine-induced decreases in BMPR2, apelin, and phospho-ERK1/2 (p<0.05). E2 protection was lost after knockdown of ERα, BMPR2, or apelin (p<0.05). ERα was necessary for E2-mediated increases in BMPR2, apelin and ERK1/2, and BMPR2 was required for the E2-mediated increase in apelin (p<0.05 for siRNA vs scramble). ERα interacted with the BMPR2 promoter. ERα, BMPR2 and apelin were unchanged in CRVH (vs control), but increased in DRVH (accompanied by an unexpected decrease in ERK1/2 activation).

Conclusions: E2, via ERα and BMPR2, increases apelin in the failing RV and in stressed cardiomyoblasts. Resistance to protective E2-ERα-BMPR2-apelin signaling may contribute to progression from CRVH to DRVH.