Abstract: 645

Urocortin-2 improves right ventricular function and attenuates experimental pulmonary arterial hypertension

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Urocortin(UCN)-2 is highly expressed in the cardiovascular system and has shown promising therapeutic effects in several studies in human and experimental heart failure. This study analysed the levels of UCN-2 in human and experimental pulmonary arterial hypertension (PAH), and the effects of UCN-2 treatment in an animal model of RV failure, secondary to PAH.

Rats were submitted to monocrotaline (MCT,n=35)/vehicle (CTRL,n=27) administration, or pulmonary artery banding (PAB,n=13)/Sham (n=5). After 14 days, animals were randomly assigned to receive either UCN-2(5μg/Kg/day) or vehicle. Functional measurements were performed 23-25days after MCT or PAB, and after euthanasia tissue was collected. Moreover, RV, lung and blood samples were collected from PAH patients(n=7) and non-PAH controls(n=6). Only significant data (mean ±SEM, p<0.05) are given.

Functional studies revealed that MCT group developed PAH, as shown by increased RV end-systolic pressure (MCT vs CTRL: 60±3 vs 22±1mmHg), end-diastolic pressure (6.0±0.7 vs 3.7±0.3mmHg), and decreased ejection fraction (32±4 vs 75±3%) and pulmonary artery acceleration time (13.6±0.57 vs 25.7±2.61ms). UCN-2 treatment attenuated these changes (48±4; 4.3±0.3mmHg; 60±3% and 20.0±1.11 ms, respectively). Also, UCN-2 treated rats had higher survival rate (76 vs 44%) and exercise capacity (MCT vs CTRL vs MCT+UCN-2: 219±88 vs 749±71 vs 573±88m). PAH rats presented RV hypertrophy as shown by the morpho-histological analysis (RV weight/tibia length ratio, MCT vs CTRL: 0.08±0.00 vs 0.04±0.00 g/cm; cardiomyocyte cross-sectional area: 353±25 vs 234±25μm²). UCN-2 therapy attenuated RV remodelling (0.06±0.00g/cm and 283±22mm², respectively). MCT-group isolated cardiomyocytes developed higher passive force compared to CTRL-group at the sarcomere lengths of 2.2 (MCT vs CTRL: 5.09±1.14 vs 2.48±0.56N/m²) and 2.3um (8.10±1.77 vs 4.02±0.82N/m²). UCN-2 restored passive force development (3.44±0.70 and 5.36±0.97N/m², respectively). Plasmatic levels of UCN-2 were increased in MCT rats with decompenated RV function, compared to compensated RV (p=0.0338). PAB rats treated with UCN-2, showed RV-specific decrease in cardiomyocyte hypertrophy (PAB vs SHAM vs PAB+UCN-2: 534±46 vs 280±29 vs 387±31μm²) and fibrosis (11.96±1.2 vs 2.23±0.3 vs 2.66±0.2%). Moreover, UCN-2 levels in the buffy coat from blood of human PAH patients were higher than in controls (p=0.035), while a trend toward an up regulation was seen in the RV and Lung of PAH patients (p=0.0663 and p=0.0734, respectively).

UCN-2 levels are altered in human and experimental PAH. UCN-2 treatment attenuates PAH and RV dysfunction and increases survival in MCT-induced PAH, and has direct anti-remodelling effects on the pressure-overloaded RV. UCN-2 has a relevant role in the pathophysiology of PAH, and might be a new treatment option in this condition.