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BOOK OF ABSTRACTS

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Neuregulin-1 treatment reduces the severity of pulmonary arterial hypertension

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Neuregulin (NRG)-1 is implicated in the preservation of left ventricular function in pathophysiological conditions [1]. However, the role of NRG-1 in right ventricular (RV) failure is still unknown. We analysed the effects of NRG-1 treatment in an animal model of pulmonary arterial hypertension (PAH) and RV heart failure (HF).

Male Wistar rats (180-200g) randomly received monocrotaline (MCT, 60mg/Kg,sc) or vehicle. After 14 days, animals randomly received NRG-1 (40µg/Kg/day,ip) or vehicle, resulting in 4 groups: ctrl (n=10); ctrl+NRG (n=10); MCT (n=10); MCT+NRG (n=10). RV hemodynamics and sample collection for vascular, morphometric, histologic and molecular studies were performed 25-28 days after MCT administration. Only significant results (mean±SEM, $p<0.05$) are given.

MCT group developed PAH, as shown by increased RV maximum pressure (MCT vs ctrl: 63±3 vs 34±3mmHg) and by decreased cardiac output (MCT vs ctrl: 34±4 vs 65±4mL/min) which were both attenuated in the MCT+NRG group (53±3mmHg and 52±2mL/min). Animals from the MCT group developed RV hypertrophy (RV weight/tibia length ratio MCT vs ctrl: 0.08±0.002 vs 0.05±0.003g/cm) and pulmonary congestion (lung weight/tibia length ratio MCT vs ctrl: 0.7±0.03 vs 0.4±0.03g/cm), both changes were minimized by the NRG-1 treatment (0.06±0.002 g/cm and 0.6±0.03 g/cm, respectively). Histological analysis also revealed a decrease of RV cardiomyocyte hypertrophy and fibrosis in the MCT+NRG group vs MCT group. The RV of MCT group presented increased expression of brain natriuretic peptide (BNP) and endothelin (ET)-1 (17.5 and 5.0 times vs ctrl, respectively). These changes were attenuated or reversed in the MCT+NRG group (BNP expression increased only 5.6 times vs ctrl, and ET-1expression did not change). The MCT group presented endothelial pulmonary dysfunction (35±2% vs ctrl 86±2% of relaxation in response to acetylcholine), which was attenuated in the MCT+NRG group (48±3%).

NRG-1 chronic treatment significantly reduced the severity of PAH and RV hypertrophy, as well as the expression of genes associated with overload and ventricular hypertrophy. These findings suggest that the NRG-1 pathway has a relevant role on the pathophysiology of PAH and RVHF, representing a potential therapeutical target.

References:

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