BOOK OF ABSTRACTS

5TH MEETING OF YOUNG RESEARCHERS OF UNIVERSITY OF PORTO

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Neuregulin attenuates pulmonary endothelial dysfunction in an experimental model of pulmonary hypertension

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Neuregulin-1 (NRG-1) is implicated in the maintenance and structural integrity of the cardiovascular system [1]. No studies have determined the effects of NRG-1 in pulmonary vasculature, in health or disease. Pulmonary arterial hypertension (PAH) is characterized by a complex proliferation and dysfunction of the endothelium and pulmonary vascular remodeling [2]. Therefore, the role of this work was to evaluate the effects of a NRG-1 chronic treatment on pulmonary endothelial dysfunction in an animal model of pulmonary arterial hypertension (PAH).

Male Wistar rats (180-200g) randomly received monocrotaline (MCT,60mg/Kg,sc) or vehicle. After 14 days, animals from these groups were randomly assigned to receive treatment with either NRG-1 (4ug/Kg/day,ip) or vehicle. The study resulted in 3 groups: control (CTRL,n=8); MCT (n=8); MCT+NRG (n=5). 21 to 24 days after MCT administration, animals were anesthetized, heart and lungs were excised *en bloc* and pulmonary arterial rings were isolated and mounted in a myograph. Endothelial function was determined by a dose-response curve to acetylcholine in phenylephrine pre-contracted rings. After the experimental protocol arterial rings were stored in formalin (10%) for histological analysis. Only significant results are presented (mean±SEM, $p<0.05$).

MCT animals presented PAH associated with endothelial dysfunction, has shown by a decreased relaxation, mediated by acetylcholine in phenylephrine pre-contracted rings, when compared with the CTRL group (MCT *vs* CTRL: 35.41±4.02% *vs* 86.27±1.85%). Treated animals (MCT+NRG) presented a significant improvement in endothelial function (48.31±5.69%). Histological analysis revealed vascular remodeling in arterial rings of MCT animals when compared with the CTRL group, as shown by an increase in tunica media thickness (MCT *vs* CTRL: 53.24±1.84mm *vs* 31.33±0.83mm), tunica media area (MCT *vs* CTRL: 104.50±7.48mm^2 *vs* 67.85±3.93mm^2) and the tunica media area/lumen area ratio (MCT *vs* CTRL: 41.23±1.48% *vs* 31.97±2.99%). Treated animals presented a significant decrease in vascular remodeling as shown by improvements in all parameters studied (34.26±0.91mm, 75.64±5.10mm^2 and 29.56±2.46% respectively).

NRG-1 chronic treatment significantly reduced the severity of PAH associated physiopathological processes, namely endothelial dysfunction and vascular remodeling. These results suggest that the NRG-1 system has a crucial role in vascular function, specifically in PAH, proving to be a potential therapeutical target.

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[2] Rhodes, C.J., Davidson, A. and Gibbs, J.S. (2009) *Therapeutic targets in pulmonary arterial hypertension*. Pharmacol Ther, 121, 69-88.