Molecular mechanisms underlying the beneficial effects of Neuregulin-1 in the treatment of Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a syndrome based on diverse etiologies, characterized by persistent increase in pulmonary vascular resistance and afterload of the right ventricle (RV), leading to failure and death. Neuregulin (NRG)-1 is associated to several physiological processes regulating cardiac development, as well as cardiac and vascular homeostasis [1]. Following the notion that NRG-1 has protective effects in the cardiovascular system the question arise whether pharmacological NRG-1/ErbB activation has any therapeutic potential in PAH and ventricular dysfunction. Thus, we aim to explore the effects of NRG-1 treatment in PAH and its impact in myocardial function, in an animal model of monocrotaline (MCT)-induced PAH. In this work, we studied molecular mechanisms underlying the beneficial effects of NRG-1 treatment of PAH.

Male Wistar rats randomly received MCT or vehicle. After 14 days, animals were arbitrarily assigned to receive NRG-1 treatment or vehicle. The study resulted in 4 groups: CTRL, CTRL+NRG-1, MCT and MCT+NRG-1. Echocardiographic, hemodynamic studies and sample collection were performed 21 to 24 days after MCT administration.

In this study we show that NRG-1 treatment is able to restore PAH-induced severe abnormalities in cardiac function and structure. Molecular studies revealed that NRG-1/ErbB system components expression in MCT animals are changed, as demonstrated with increased levels of NRG-1 and decreased levels of ErbB4 receptors that were reversed by NRG-1 treatment. We also found increased levels of ErbB2 receptors, ADAM-17, ADAM-19, and increased eNOS expression in the RV of MCT and MCT+NRG-1 animals. NRG-1 treatment reversed changes in glucose transporters and in markers of apoptosis, as well as decreased the expression of IL6 and TNF-α found in MCT group. Moreover, we found that the increased expression of BNP, ET-1 and HIF is attenuated or reversed with NRG-1 therapy.

Concluding, we show that NRG-1 treatment might decrease PAH, restore cardiopulmonary function and attenuate or reverses the expression of markers of cardiac overload, hypertrophy and hypoxia. These beneficial effects of NRG-1 are associated with the modulation of different signaling pathways, namely apoptotic, metabolic, survival/ proliferation, and inflammation pathways.

[1] Mendes-Ferreira, P., De Keulenaer, G. W., Leite-Moreira, A. F., & Brás-Silva, C. (2013). *Therapeutic potential of neuregulin-1 in cardiovascular disease*. Drug discovery today, 18(17-18), 836–42.