Modulation of right ventricle function by Neuregulin-1 - therapeutic implications in pulmonary hypertension

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Neuregulin (NRG)-1 is implicated in the preservation of left ventricular (LV) performance in pathophysiological conditions [1]. Nevertheless, the role of NRG-1 in right ventricular (RV) failure secondary to pulmonary arterial hypertension (PAH) remains unknown. The main goal of this study was to investigate the effects of NRG-1 treatment in PAH and its repercussion in myocardial function, in an animal model of monocrotaline (MCT)-induced PAH. In order to distinguish indirect from direct myocardial effects, we also used a rat model of RV hypertrophy without PAH (banding of the pulmonary artery - PAB) [2].

Seven-week-old male Wistar rats randomly received a subcutaneous injection of MCT (60 mg/kg) or an equal volume of vehicle. Additionally, another set of rats were subjected to PAB or sham operation. Fourteen days after surgery or MCT injection, rats were arbitrarily assigned to receive therapy with NRG-1 (40µg/Kg/day) or vehicle. The study resulted in 8 experimental groups: CTRL (n=24), CTRL+NRG-1 (n=13), MCT (n=21), MCT+NRG-1 (n=24), SHAM (n=7), SHAM+NRG-1 (n=5), BAND (n=5) and BAND+NRG-1 (n=5). Echocardiographic, hemodynamic studies and sample collection were performed 21 to 24 days after MCT administration or PAB surgery.

MCT animals developed PAH, demonstrated by impaired pulmonary flow, increased RV systolic pressures and decreased cardiac output. The increase in cardiomyocyte passive tension, observed in the MCT group, were both reduced in the MCT+NRG-1 group. Administration of MCT resulted in RV hypertrophy, both at the whole heart and at the cardiomyocyte level, simultaneous with increased fibrosis. MCT animals treating with NRG-1 decreased overall hypertrophy and fibrosis. Moreover, NRG-1 treatment also improved ventricular function and reverted RV morphohistological changes in animals submitted to PAB.

In conclusion, we show that NRG-1 treatment is able to restore PAH-induced severe abnormalities in cardiopulmonary function, having also cardiac-specific effects in myocardium. These results suggest that the NRG-1 pathway has a relevant role in the pathophysiology of PAH and right ventricular dysfunction, representing a potential therapeutic target in these conditions.

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[2] Schafer, S., Ellinghaus, P. and Janssen, W. (2009), *Chronic inhibition of phosphodiesterase 5 does not prevent pressure-overload-induced right-ventricular remodeling,* Cardiovascular Research, 82(1), 30-9.