DYSREGULATION OF LET-7/NGF/MIR-21 AXIS IN PULMONARY ARTERY OF MONOCROTALINE-INDUCED PULMONARY HYPERTENSION IN RATS

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Objective: MicroRNAs are small, non-coding molecules that are able to modulate gene expression and have been involved in many different pathologies. Increased levels of nerve growth factor (NGF) were described to play a role in the development and persistence of pulmonary hypertension and this growth factor is known to be downregulated by let-7 family of microRNAs. Furthermore, NGF can affect expression of certain microRNAs as well, namely miR-21 which was shown to be upregulated after NGF stimulation in neuronal cells. miR-21 is known to stimulate remodelling of pulmonary vascular bed and moreover, further supports NGF signalling. In this study, we examined the expression of aforementioned microRNAs and NGF and their potential role in pathophysiology of experimental model of monocrotaline-induced PH.
Design and method: 12-week old male Wistar rats were injected either with monocrotaline (MCT group, s.c. 60 mg/kg) or vehicle (CON group). 4-weeks after the treatment, rats were sacrificed and the expression of let-7 family, NGF and miR-21 was determined in pulmonary artery (PA), lungs, and right ventricle (RV) by qRT-PCR.
Results: In the let-7 family, we noted significant decrease of let-7g and let-7i expression in PA (-31% and -34% respectively, $P<0.05$ vs CON) and significant increase of miR-98 expression in RV (+23%, $P<0.05$ vs CON). NGF gene was significantly increased only in PA (+106, $P<0.05$ vs CON), there were no significant changes in lungs or RV. In the miR-21 expression, we noted significant increase in both PA and lungs (+37% and +92% respectively, $P<0.05$ vs CON).
Conclusion: The downregulation of the components of let-7 family was in consonance with increased expression of NGF and miR-21 in PA. We did not observe the dysregulation of this axis in other organs of interest and based on these results, we conclude that let-7/NGF/miR-21 axis could be one of the key pathways contributing to the pulmonary vascular pathophysiology in experimental model of MCT-induced PH.