

ABSTRACT

BENEFICIAL EFFECTS OF GHRELIN ADMINISTRATION IN A PAEDIATRIC MODEL OF PULMONARY HYPERTENSION INDUCED BY MONOCROTALINE

INTRODUCTION: Pulmonary hypertension (PH) is characterized by structural changes of the pulmonary vessels as well as right ventricular (RV) hypertrophy. The reversibility of pulmonary vascular remodelling is possible only at paediatric ages. The characterization of the infantile PH model will allow the study of pathophysiology of this disease and to test the effects of new drugs. Ghrelin (Ghr) is a new vasoactive peptide with several cardiovascular effects.

AIM: Establish a paediatric MCT-induced PH model and to evaluate hemodynamic and morphometric effects of administration of Ghr.

METHODS: In order to establish a pediatric model of PH induced by MCT, *Wistar* rats were injected with different doses of MCT (60 mg/Kg, 50 mg/Kg, 30 mg/Kg) and survival was evaluated at 21 days of life. In order to evaluate the effects of Ghr, *Wistar* rats with 8-day-old randomly received MCT (30mg/Kg, subcutaneous) or equal volume of vehicle (Group Ctrl, n=10). At D7 (15 days of life), animals treated with MCT randomly received Ghr (100g/kg, subcutaneous, bid) (Group MCT-Ghr, n=10) or vehicle (Group MCT, n=8) for 2 weeks. At D21 (29 days of life), animals were instrumented to record several biventricular hemodynamic parameters. At the end, heart and lungs were excised and weighted.

RESULTS: A paediatric model of PH induced by MCT was established using half dose (30 mg/Kg) used in the adult animal. MCT group animals had an inferior weight when compared with control group. Animals treated with Ghr had an increase in weight. Heart and lung weights were increased in the MCT group comparing with the control

group. Ghr administration attenuated MCT effects on heart and lung weights. Right ventricle peak systolic pressure was increased in the MCT group and treatment with Ghr significantly decreased the degree of PH. In the MCT group, peak rates of ventricular pressure (dP/dT_{max}) were increased and were reduced in the Ghr group. In the MCT group occurred diastolic dysfunction translated by an increase in τ (tau, time constant inversely related with myocardial relaxation rate) and end-diastolic pressure in the RV. In the Ghr group occurred significant decrease in the myocardial relaxation rate and end-diastolic pressure. There no significant differences between hemodynamic data related with the left ventricle (LV).

DISCUSSION AND CONCLUSIONS: Was characterized, for the first time, the biventricular hemodynamics of Wistar rats in paediatric age and was established a model of paediatric PH induced by MCT. Animals treated with MCT presented RV hypertrophy, PH and diastolic dysfunction (elevation of end-diastolic pressure; slower myocardial relaxation rate) in RV. Ghrelin administration ameliorated PH and RV hemodynamics. These beneficial effects of GHR open new therapeutic options for this disease in paediatric population.