HYPOXIC HEART REMODELING AND MOLECULAR MECHANISMS OF CARDIOPROTECTION

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Hypoxia induced pulmonary vasoconstriction leads to right heart remodeling. Molecular mechanisms responsible for physiological or pathological remodeling, as well as protecting heart from failure development, are incompletely known. The aim of the investigation was to characterize heart remodeling development and induction of cardioprotective mechanisms in myocardium under chronic hypoxia conditions. In male Wistar rats acclimatized to high altitude hypoxia (2100 m), hearts and lung fragments were excised under urethane narcosis and morphologically estimated. Some animals were exposed acute hypobaric hypoxia séance in barochamber (5600 m during 3 h). In both groups, expression of hypoxia inducible transcription factor (HIF) subunits and insulin-like growth factor-1 (IGF-1) mRNA, heat shock proteins (HSP) in tissues was assessed by RT-PCR and Western blotting. It was shown that hypoxia adapted animals had marked right heart hypertrophy, RV/(LV+RV) mass ratio was increased by 48% in comparison to nonhypoxic (sea level) rats. Besides, lung vessel remodeling was found, indicating pulmonary hypertension. Due to inhibitory properties of HIF-3alpha subunit to HIF-1/2alpha DNA binding, we specially estimated HIF subunit expression ratio as possible key point for remodeling control. It was found, that HIF-3alpha/HIF-1alpha mRNA expression ratio was 4.65-fold elevated in the right ventricles under chronic hypoxia, and 7.76-fold - in the left ones. These data can evidence that HIF-1alpha mediated gene induction in adapted myocardium was becoming strongly limited. Accordingly, expression of IGF-1 gene, known as associated with heart failure development in human, was decreased in both heart ventricles. However, in the hypertrophied right ventricles, expression of HSP70 family proteins was 6.5-fold increased that provided synthesis and restoration of tissue proteins. For testing of changes in hypoxic reactivity, we assessed gene induction in adapted hearts in response to acute hypoxia. In 24 h after the hypoxic séance, we found further increase HIF-3alpha/HIF-1alpha ratio in the right ventricles, and strong HSP70 family proteins induction in both heart ventricles. At the same time, HSP60 - IGF-1 mediated mechanism of heart remodeling was not found markedly induced by acute hypoxia. Taken together, these molecular changes mediate intensified tissue protection from hypoxic injury in adapted heart, and provide its higher functional loading under hypoxic conditions with strong limitation of HIF-mediated gene induction and tissue remodeling. Our results may evidence that myocardial adaptation to chronic hypoxia involves genetic and molecular mechanisms to protect heart from pathological remodeling and failure development. The value of HIF-3alpha/HIF-1alpha mRNA expression ratio may serve as criterion to estimate tissue remodeling risk under hypoxia.