Pathophysiology of hypoxia

SHIFT OF REGULATORY PATHWAYS IN EARLY AND EXTENDED STAGE OF MYOCARDIAL HYPERTROPHY

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Question. Hypertension in pulmonary or systemic circulation leads to hypertrophy of right or left heart ventricle, respectively. However, the similarities or differences in the mechanisms of cardiac remodeling of various genesis are insufficient elucidated. The aim of the investigation was to determine prohypertrophic and metabotropic gene based mechanisms of myocardial remodeling owing to chronic hypoxia, adrenergic stimulation or high-cholesterol diet in rats. **Methods.** For pulmonary overload, male Wistar rats were adapted to chronic hypoxia at an altitude of 2100 m above sea level. For systemic circulation influence, other groups of rats, Wistar and SHR, were treated with low doses of isoproterenol or exposed to high-cholesterol diet. Tissue samples were excised from anesthetized animals in dynamics, and subjected to morphological evaluation. Myocardial expression levels of mRNA and microRNA were estimated by real-time PCR, expression and phosphorylation of proteins - by Western blotting. **Results.** It was shown that hypoxia exposed animals had marked right heart hypertrophy and lung vessel remodeling, accompanied with translational stimulation of prohypertropic kinase Akt/PKB. Short-term hypoxic influences (3-5 days) resulted in induction of insulin-like growth factor (IGF)-1, Akt and its phosphorylation. However, in chronic hypoxia, gene and protein expression of IGF-1, key inductor of Akt-mediated signaling, was strongly inhibited. In like manner, 3-7 days of adrenergic stimulation in Wistar rats led to the left ventricle hypertrophy with induction of IGF-1/Akt-signaling, but chronically hypertensive SHR were characterized by repression of *IGF-1* gene in spite of strong left ventricle hypertrophy. It was shown that such *IGF-1* reduction was accompanied with high miR-1 expression in myocardium. Similarly, Wistar rats demonstrated stronger responsibility to prolonged cholesterol administration, and changes in expression of metabotropic transcription factors SREBP-1 and -2 mRNA, than SHR. **Conclusions.** Thus, cardiac ventricular hypertrophy, induced by hypoxic pulmonary hypertension or systemic vasoconstriction, has some similar molecular mechanisms. Right or left ventricle hypertrophy may be initially mediated by induction of IGF-1 in myocardium, and stimulation of IGF-1/Akt-mediated prohypertrophic signaling. In chronic influences, this signaling appears to be limited by inhibitory action of miR-1 on IGF-1 to reduce excessive myocardial growth. In the same time, initial stimulation of carbohydrate utilization in overloaded myocardial tissue is replaced by long-term up-regulation of lipid metabolism.