Carvedilol modulates the expression of hypoxia-inducible factor-1alpha and vascular endothelial growth factor in a rat model of volume-overload heart failure

徐國基

Shyu KG;Lu MJ;Chnag H;Sun HY;Wang BW;Kuan P

摘要

Abstract

BACKGROUND: The use of beta-blockers has emerged as a beneficial treatment for congestive heart failure. Hypoxia-inducible factor-1alpha (HIF-1alpha) is tightly regulated in the ventricular myocardium. However, the expression of HIF-1alpha in chronic heart failure resulting from volume overload and after treatment with beta-blocker is little known. METHODS AND RESULTS: To test the hypothesis that HIF-1alpha plays a role in the failing myocardium because of volume overload, an aorta-caval shunt was created for 4 weeks in adult Sprague-Dawley rats to induce volume-overload heart failure. Carvedilol at 50 mg/kg body weight per day after surgery was given. The heart weight and body weight ratio increased from 2.6 +/- 0.3 in the sham group to 3.9 +/- 0.7 ($P < .001$) in the shunt group. Left ventricular end-diastolic dimension increased from 6.5 +/- 0.5 mm to 8.7 +/- 0.6 mm ($P < .001$). Treatment with carvedilol in the shunt group reversed the heart weight and ventricular dimension to the baseline values. Western blot showed that HIF-1alpha, vascular endothelial growth factor (VEGF), and brain natriuretic peptide (BNP) proteins were upregulated and nerve growth factor-beta (NGF-beta) downregulated in the shunt group. Real-time polymerase chain reaction showed that mRNA of HIF-1alpha, VEGF, and BNP increased and mRNA of NGF-beta decreased in the shunt group. Treatment with carvedilol reversed both protein and mRNA of HIF-1alpha, VEGF, BNP, and NGF-beta to the baseline values. Increased immunohistochemical labeling of HIF-1alpha,

VEGF, and BNP in the ventricular myocardium was observed in the shunt group and carvedilol again normalized the labeling. CONCLUSION: HIF-1alpha and VEGF mRNA and protein expression were upregulated in the rat model of volume-overload heart failure. Treatment with carvedilol is associated with a reversal of abnormal regulation of HIF-1alpha and VEGF in the failing ventricular myocardium.