Basic Science and Experimental Studies

Carvedilol Modulates the Expression of Hypoxia-Inducible Factor-1α and Vascular Endothelial Growth Factor in a Rat Model of Volume-Overload Heart Failure

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ABSTRACT

Background: The use of β-blockers has emerged as a beneficial treatment for congestive heart failure. Hypoxia-inducible factor-1α (HIF-1α) is tightly regulated in the ventricular myocardium. However, the expression of HIF-1α in chronic heart failure resulting from volume overload and after treatment with β-blocker is little known.

Methods and Results: To test the hypothesis that HIF-1α 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-1α, vascular endothelial growth factor (VEGF), and brain natriuretic peptide (BNP) proteins were upregulated and nerve growth factor-β (NGF-β) downregulated in the shunt group. Real-time polymerase chain reaction showed that mRNA of HIF-1α, VEGF, and BNP increased and mRNA of NGF-β decreased in the shunt group. Treatment with carvedilol reversed both protein and mRNA of HIF-1α, VEGF, BNP, and NGF-β to the baseline values. Increased immunohistochemical labeling of HIF-1α, VEGF, and BNP in the ventricular myocardium was observed in the shunt group and carvedilol again normalized the labeling.

Conclusion: HIF-1α 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-1α and VEGF in the failing ventricular myocardium.

Key Words: β-blocker, congestive heart failure, gene expression, growth factor.

Congestive heart failure is an important cause of death in human. How to prevent and treat heart failure is a critical issue in medicine. In heart failure, key enzymes in β-oxidation are downregulated, with impaired incorporation of fatty acid as a substrate for β-oxidation.[1,2] In the mechanism of the activation of glycolysis, hypoxia-inducible factor-1α (HIF-1α) is known to be involved in the increased expression of glycolytic enzymes.[3,4] In the progression of heart failure, in which impaired energy metabolism may occur, HIF-1α is likely to be involved in the activation of the glycolytic system. HIF-1α has been shown to early express in ischemic myocardium in patients with myocardial infarction[5] and in animal model of coronary artery ligation.[6]

In addition to the hypoxic pathway mediating HIF-1α expression, other, nonhypoxic pathways factors such as neurohormonal activators and mechanical stress have also been shown to induce HIF-1α expression in vascular smooth cells.[7,8] Recently Kim et al[9] demonstrated that acute hemodynamic overload induced HIF-1α and vascular endothelial growth factor (VEGF) expression in rat myocardium.

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