Carvedilol, a pharmacological antioxidant, inhibits neointimal matrix metalloproteinase-2 and -9 in experimental atherosclerosis.

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摘要

Abstract

Matrix metalloproteinase (MMP) is critical to the progression of atherosclerosis and neointima hyperplasia after vascular injury. We investigated the effects of carvedilol, a pharmacological antioxidant with alpha- and beta-adrenergic blocking activity, on MMP-2 and MMP-9 expression. Vascular injury was induced with the balloon catheters on abdominal aortas of high-cholesterol-fed rabbits. On Day 21, there was significant aortic neointima formation with increased oxidative DNA damage by immunostaining with 8-hydroxy-2'-deoxyguanosine and enhanced MMP-2 and MMP-9 expressions by Western blotting, which were significantly reduced by oral administration of carvedilol (20 mg/kg/day) or probucol (100 mg/kg/day). Vascular expression (by Western blot), activity (by gelatin zymography), and mRNA levels of MMP-2 and MMP-9 were also reduced by carvedilol or probucol. Besides, pretreatment with carvedilol or probucol but not propranolol, a beta-blocker, or prazocin, an alpha-blocker, inhibited tumor necrosis factor-alpha-stimulated expressions and activities of MMP-2 and MMP-9 in human aortic smooth muscle cells. On electrophoretic mobility-shift assay, carvedilol inhibited the binding activities of activator protein-1 and specific protein-1, two major transcription factors for MMP promoter regions. Accordingly, carvedilol, a pharmacological antioxidant, inhibited in vivo and in vitro expression of MMP-2 and MMP-9 properly by modulating the redox-related pathways, suggesting its potential clinical implications.