Additive effects of combined blockade of AT1 receptor and HMG-CoA reductase on left ventricular remodeling in infarcted rats.

張念中;李聰明
Lee Tsung-Ming;Lin Mei-Shu;Chou Tsai-Fwu;Chang Nen-Chung

摘要

Abstract

Both angiotensin receptor antagonists and 3-hydroxy-3- methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been shown to attenuate cardiomyocyte hypertrophy after myocardial infarction. Whether combination treatment may be superior to either drug alone on cardiomyocyte hypertrophy remains unclear. After ligation of the left anterior descending artery, rats were randomized to both, one, or neither of the angiotensin receptor antagonists olmesartan (0.01, 0.1, 1, and 2 mg(.)kg(-1.)day(-1)) and HMG-CoA reductase inhibitor pravastatin (5 mg(.)kg(-1.) day(-1)) for 4 wk. Each drug, when given alone, decreased cardiomyocyte sizes isolated by enzymatic dissociation at the border zone when compared with vehicles. However, compared with either drug alone, combined olmesartan and pravastatin prevent cardiomyocyte hypertrophy to a larger extent, which was further confirmed by downregulation of the left ventricular atrial natriuretic peptide mRNA. The myocardial endothelin-1 levels at the border zone were 6.5-fold higher ($P < 0.0001$) in the vehicle group compared with the sham group, which can be inhibited after pravastatin administration. Combination treatment significantly attenuated cardiomyocyte hypertrophy in a dose-dependent manner, although tissue endothelin-1 levels remained stable in combination groups of different olmesartan doses. Measurements of the arrhythmic score mirrored those of cardiomyocyte hypertrophy. Dual therapy with pravastatin and olmesartan, which produced an additive reduction in cardiomyocyte hypertrophy and cardiac fibrosis after myocardial infarction through different mechanisms, decreases the propensity of the heart to arrhythmogenesis. Pravastatin administration provided favorable ventricular remodeling, probably through decreased tissue endothelin-1 level. In contrast, olmesartan-related attenuated cardiomyocyte hypertrophy is independent of endothelin-1 pathway..