Effects of pravastatin on ventricular remodeling by activation of myocardial K-ATP channels in infarcted rats: role of 70-KDa S6 kinase

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摘要

Abstract

Reactive cardiomyocyte hypertrophy after myocardial infarction is an important risk factor for arrhythmias. Myocardial ATP-sensitive potassium (K(ATP)) channels have been implicated in attenuating cardiac hypertrophy by inhibition of 70-kDa S6 kinase. We investigated the effect of pravastatin on ventricular hypertrophy during remodeling after myocardial infarction and whether the attenuated hypertrophic effect was via activation of myocardial K(ATP) channels. Twenty-four hours after ligation of the anterior descending artery, male Wistar rats were randomized to either vehicle, nicorandil (an agonist of K(ATP) channels), pravastatin, glibenclamide (an antagonist of K(ATP) channels), or a combination of nicorandil and glibenclamide or pravastatin and glibenclamide for 4 weeks. Infarct size and mortality were similar among the infarcted groups. Cardiomyocyte sizes isolated by enzymatic dissociation after infarction significantly increased at the border zone in vehicle-treated infarcted rats compared with sham-operated rats. Rats in the nicorandil- and pravastatin-treated groups significantly attenuated cardiomyocyte hypertrophy, as compared with the vehicle-treated group. Arrhythmic scores during programmed stimulation mirrored those of cardiomyocyte hypertrophy. Increased 70-kDa S6 kinase mRNA expression in cardiac remodeling was confirmed by reverse transcription-polymerase chain reaction, consistent with the results of immunohistochemistry and Western blot for the phosphorylation of 70-kDa S6 kinase. Nicorandil-induced effects were abolished by administering glibenclamide. Similarly, the beneficial effects of pravastatin were abolished by administering glibenclamide, implicating K(ATP) channels as the relevant target. Activation of K(ATP) channels by pravastatin administration can attenuate ventricular remodeling through a S6 kinase-dependent pathway after infarction.