Effect of ATP-sensitive potassium channel agonists on ventricular remodeling in healed rat infarcts

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摘要

Abstract

Objectives The purpose of this study was to determine whether ATP-sensitive potassium (KATP) channel agonists exert a beneficial effect on the structural, functional, and molecular features of the remodeling heart in infarcted rats. Background Myocardial KATP channels have been implicated in the ventricular remodeling after myocardial infarction by inhibition of 70-kDa S6 (p70S6) kinase. Methods Male Wistar rats after induction of myocardial infarction were randomized to either vehicle, agonists of KATP channels nicorandil and pinacidil, an antagonist of KATP channels glibenclamide, or a combination of nicorandil and glibenclamide or pinacidil and glibenclamide for 4 weeks. To verify the role of p70S6 kinase in ventricular remodeling, rapamycin was also assessed. Results Significant ventricular hypertrophy was detected by increased myocyte size at the border zone isolated by enzymatic dissociation after infarction. Increased synthesis of p70S6 kinase messenger ribonucleic acid after infarction in vehicle-treated rats was confirmed by reverse transcription-polymerase chain reaction, consistent with the results of immunohistochemistry and Western blot for phosphorylated p70S6 kinase. Rats in the nicorandil- and pinacidil-treated groups significantly attenuated cardiomyocyte hypertrophy and phosphorylated p70S6 kinase expression with similar potency, as compared with vehicle. The beneficial effects of nicorandil and pinacidil were abolished by administering either glibenclamide or 5-hydroxydecanoate. Addition of rapamycin attenuated ventricular remodeling and did not have additional, beneficial effects compared with those seen in rats treated with either nicorandil or pinacidil alone. Conclusions Activation of KATP channels by either nicorandil or pinacidil can attenuate ventricular remodeling, probably through a p70S6 kinase-dependent pathway after infarction..