Effect of pravastatin on sympathetic reinnervation in post-infarcted rats

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摘要

Abstract

We assessed whether pravastatin attenuates cardiac sympathetic reinnervation after myocardial infarction through the activation of ATP- sensitive K+ (K-ATP) channels. Epidemiological studies have shown that men treated with statins appear to have a lower incidence of sudden death than men without statins. However, the specific factor for this has remained disappointingly elusive. Twenty-four hours after ligation of the anterior descending artery, male Wistar rats were randomized to groups treated with either vehicle, nicorandil (a specific mitochondrial KATP channel agonist), pinacidil (a nonspecific KATP channel agonist), pravastatin, glibenclamide (a KATP channel blocker), or a combination of nicorandil and glibenclamide, pinacidil and glibenclamide, or pravastatin and glibenclamide for 4 wk. Myocardial norepinephrine levels revealed a significant elevation in vehicle-treated rats at the remote zone compared with sham-operated rats (2.54 +/- 0.17 vs. 1.26 +/- 0.36 mu g/g protein, $P < 0.0001$), consistent with excessive sympathetic reinnervation after infarction. Immunohistochemical analysis for tyrosine hydroxylase, growth- associated factor 43, and neurofilament also confirmed the change of myocardial norepinephrine. This was paralleled by a significant upregulation of tyrosine hydroxylase protein expression and mRNA in vehicle-treated rats, which was reduced after the administration of either nicorandil, pinacidil, or pravastatin. Arrhythmic scores during programmed stimulation in vehicle-treated rats were significantly higher than those treated with pravastatin. In contrast, the beneficial effects of pravastatin were reversed by the addition of glibenclamide, implicating K-ATP channels as the relevant target. The sympathetic reinnervation after infarction is modulated by the activation of K-ATP channels. Chronic use of pravastatin after infarction, resulting in attenuated sympathetic reinnervation by the activation of K-ATP channels, may modify the arrhythomogenic response to programmed electrical stimulation