Effect of Pravastatin on Sympathetic Hyperinnervation in Post-infarcted Rats

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OBJECTIVES We assessed whether pravastatin attenuates the regeneration of cardiac sympathetic nerves after myocardial infarction through activation of ATP-sensitive potassium (K_{ATP}) channels.

BACKGROUD Epidemiologic studies showed that men treated with statins appear to have a lower incidence of sudden death than men without statins. However, the specific factors for this have remained disappointingly elusive.

METHODS 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. Sham operation served as controls.

RESULTS Measurement of 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 μg/g protein, $p < 0.0001$), consistent with sympathetic hyperinnervation after infarction. Myocardial norepinephrine levels were blunted after administering either pravastatin or nicorandil. Immunohistochemical analysis and Western blot of tyrosine hydroxylase confirmed the change of myocardial norepinephrine. This was paralleled by a 7.3 ± 2.1-fold upregulation of tyrosine hydroxylase mRNA assessed by real-time quantitative RT-PCR in the vehicle-treated rats, which reduced after administering either pravastatin or nicorandil. Arrhythmic scores during programmed stimulation in the vehicle-treated rats were significantly higher than those treated with pravastatin. In contrast, the beneficial effects of pravastatin-induced were reversed by the addition of glibenclamide, implicating K_{ATP} channels as the relevant target.

CONCLUSIONS The sympathetic reinnervation after infarction is modulated by

activation of K_{ATP} channels. Chronic use of pravastain after infarction, resulting in attenuated sympathetic innervation by activation of K_{ATP} channels, may modify the arrhythomogenic response to programmed electrical stimulation.