

Effect of endothelin receptor antagonists on ventricular susceptibility in postinfarcted rats

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摘要

Abstract

This study investigated whether selective endothelin (EI) type A (ETA) or nonselective ETA/ETB receptor blockade exerted antiarrhythmic effects through attenuated sympathetic reinnervation after infarction. Twenty-four hours after ligation of the left anterior descending artery, male Wistar rats received either vehicle, ABT-627 (selective ETA receptor antagonist), bosentan (nonselective ETA/ETB receptor antagonist), or hydralazine for 4 wk. The measurement of myocardial ET-1 levels at the remote zone revealed a significant increase in vehicle-treated infarcted rats compared with sham-operated rats, consistent with increased activities of ET-1 after infarction. Sympathetic nerve function changes assessed by the norepinephrine content of myocardium and the dialysate and plasma dihydroxyphenylglycol levels were parallel to ET-1 levels. Immunohistochemical analysis for tyrosine hydroxylase, growth-associated protein 43, and neurofilament also confirmed the change of nerve function. This was accompanied with a significant upregulation of nerve growth factor protein expression and mRNA in the vehicle-treated infarcted rats, which reduced after the administration of either ETA or ETA/ETB blockade to a similar extent. The beneficial effects of ET receptor antagonists on sympathetic nerve function and structures were dissociated from their blood pressure-lowering effect because ET receptor antagonists and hydralazine reduced arterial pressure similarly. Arrhythmic severity during programmed stimulation in ET receptor antagonists-treated rats was significantly lower than that in vehicle-treated infarcted rats. Our data indicate that the ET system, especially via ETA receptors, plays an important role in attenuating sympathetic reinnervation after infarction. Independent of their hemodynamic effects, a chronic use of either ETA or ETA/ETB antagonists may modify the arrhythmogenic response to programmed electrical stimulation