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A small non-erythropoietic helix B surface peptide based upon erythropoietin structure is cardioprotective against ischemic myocardial damage.

Ahmet I, Tae HJ, Juhaszova M, Riordon D, Boheler K, Sollott SJ, Brines M, Cerami A, Lakatta EG, Talan MI.

Laboratory of Cardiovascular Sciences, National Institute on Aging, NIH, Baltimore, MD;

Abstract

Strong cardioprotective properties of erythropoietin (EPO), reported over the last 10 years, have been difficult to translate to clinical applications for ischemic cardioprotection due to undesirable parallel activation of erythropoiesis and trombogenesis. A pyroglutamate helix B surface peptide (pHBP), recently engineered to include only a part of the EPO molecule that does not bind to EPO receptor and thus, is not erythropoietic, retains tissue protective properties of EPO. Here we compared the ability of pHBP and EPO to protect cardiac myocytes from oxidative stress in vitro and cardiac tissue from ischemic damage in vivo.HBP, similar to EPO, increased the reactive oxygen species threshold for induction of the mitochondrial permeability transition by 40%. In an experimental model of myocardial infarction, induced by permanent ligation of a coronary artery in rats, a single bolus injection of 60 _g/kg of pHBP immediately after coronary ligation, similar to EPO, reduced apoptosis in the myocardial area at risk, examined 24 h later, by 80% and inflammation by 34%. Myocardial infarction (MI) measured 24 hrs after coronary ligation also was similarly reduced by 50% in both pHBP and EPO treated rats. Two weeks after surgery left ventricular remodeling (ventricular dilation) and functional decline (fall in ejection fraction), assessed by echocardiography, were significantly and similarly attenuated in HBP- and EPO-treated rats, and MI size was reduced by 25%. The effect was retained during the 6-wk follow-up. A single bolus injection of pHBP immediately after coronary ligation was effective in reduction of MI size in a dose as low as 1 _g/kg, but was ineffectiveness at a 60 _g/kg dose, if administered 24 hrs after MI induction.We conclude that pHBP is equally cardioprotective with EPO and deserves further consideration as a safer alternative to rhEPO in the search of therapeutic options to reduce myocardial damage following blockade of the coronary circulation.