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Cardioprotection by a nonerythropoietic, tissue-protective peptide mimicking the 3D structure of erythropoietin.

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Abstract

Erythropoietin (EPO), originally identified for its critical hormonal role in regulating production and survival of erythrocytes, is a member of the type 1 cytokine superfamily. Recent studies have shown that EPO has cytoprotective effects in a wide variety of tissues, including the heart, by preventing apoptosis. However, EPO also has undesirable effects, such as thrombogenesis. In the present study, we investigated whether a helix B-surface peptide (HBSP), a nonerythropoietic, tissue-protective peptide mimicking the 3D structure of erythropoietin, protects cardiomyocytes from apoptosis in vitro and in vivo. In cultured neonatal rat cardiomyocytes, HBSP clearly inhibited apoptosis (approximately 80%) induced by TNF-alpha, which was comparable with the effect of EPO, and activated critical signaling pathways of cell survival, including Akt, ERK1/2, and STAT3. Among these pathways, Akt was shown to play an essential role in HBSP-induced prevention of apoptosis, as assessed by using a small interfering RNA approach. In the dilated cardiomyopathic hamster (J2N-k), whose cardiac tissues diffusely expressed TNF-alpha, HBSP also inhibited apoptosis (approximately 70%) and activated Akt in cardiomyocytes. Furthermore, the levels of serum creatine kinase activity and of cardiac expression of atrial natriuretic peptide, a marker of chronic heart failure, were down-regulated in animals treated with HBSP. These data demonstrate that HBSP protects cardiomyocytes from apoptosis and leads to a favorable outcome in failing hearts through an Akt-dependent pathway. Because HBSP does not have the undesirable effects of EPO, it could be a promising alternative for EPO to treat cardiovascular diseases, such as myocardial infarction and heart failure.