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Nonerythropoietic, tissue-protective peptides derived from the tertiary structure of erythropoietin.

Brines M, Patel NS, Villa P, Brines C, Mennini T, De Paola M, Erbayraktar Z, Erbayraktar S, Sepodes B, Thiemermann C, Ghezzi P, Yamin M, Hand CC, Xie QW, Coleman T, Cerami A.

Warren Pharmaceuticals, Ossining, NY 10562, USA. mbrines@warrenpharma.com

Abstract

Erythropoietin (EPO), a member of the type 1 cytokine superfamily, plays a critical hormonal role regulating erythrocyte production as well as a paracrine/autocrine role in which locally produced EPO protects a wide variety of tissues from diverse injuries. Significantly, these functions are mediated by distinct receptors: hematopoiesis via the EPO receptor homodimer and tissue protection via a heterocomplex composed of the EPO receptor and CD131, the beta common receptor. In the present work, we have delimited tissue-protective domains within EPO to short peptide sequences. We demonstrate that helix B (amino acid residues 58-82) of EPO, which faces the aqueous medium when EPO is bound to the receptor homodimer, is both neuroprotective in vitro and tissue protective in vivo in a variety of models, including ischemic stroke, diabetes-induced retinal edema, and peripheral nerve trauma. Remarkably, an 11-aa peptide composed of adjacent amino acids forming the aqueous face of helix B is also tissue protective, as confirmed by its therapeutic benefit in models of ischemic stroke and renal ischemia-reperfusion. Further, this peptide simulating the aqueous surface of helix B also exhibits EPO's trophic effects by accelerating wound healing and augmenting cognitive function in rodents. As anticipated, neither helix B nor the 11-aa peptide is erythropoietic in vitro or in vivo. Thus, the tissue-protective activities of EPO are mimicked by small, nonerythropoietic peptides that simulate a portion of EPO's three-dimensional structure.