INTRODUCTION

The mitochondrial protein frataxin (FXN) is a chaperone involved in assembly of iron-sulfur clusters in the mitochondria. Decreased FXN gene expression causes iron accumulation, oxidative stress and cell damage. Drugs that can increase frataxin levels offer a possible therapy for diseases caused by reduced expression levels of FXN. Recombinant human erythropoietin (rhEPO) has recently been shown to increase protein levels of FXN in fibroblasts from human patients in vitro (1,2).

EPO is a hormone that stimulates and regulates the production of red blood cells. EPO, the EPO receptor (EPOR) and the soluble EPO-R (EPOR-S) are also expressed in brain and retinal tissue. In the retina, EPO and EPOR are mainly found in/on retinal ganglion cells (RGCs) and on glia. EPO acts as a potent neuroprotective peptide and protects cells against oxidative damage. The non-erythropoietic carbamoylated derivative (CEPO) has also been shown to be neuroprotective. EPO and its analogues represent putative therapeutic agents for the treatment of several neurodegenerative pathologies.

AIM OF THE STUDY

Aims of this study are: 1) to evaluate neuroprotective effects of EPO and CEPO in the retina after transient retinal ischemia/reperfusion (TRI) in vivo, and 2) to examine whether FXN is involved in EPO and CEPO-mediated neuroprotection in vivo.

RESULTS

RGC survival is significantly increased by rhEPO/CEPO treatment after transient retinal ischemia (TRI) 14 days post ischemia

A significantly increased pFXN and decreased EPOR-S protein expression was observed after TRI in vivo

CONCLUSIONS

- Treatment with rhEPO or its derivative CEPO has an neuroprotective effect on retinal ganglion cells after transient retinal ischemia in vivo (HIC).
- The retinal EPO/EPOR pathway becomes modulated after TRI, as indicated by an increase in endogenous EPO expression 12h post ischemia, and a EPOR-S down regulation (WB). EPO/EPOR mRNA expression does not change (not shown).
- Treatment with rhEPO or CEPO does not alter mRNA expression for EPOR or endogenous EPO (RT-PCR).
- The mRNA and protein expression of the mitochondrial protein frataxin is up-regulated after ischemia with a maximum 12h post lesion.
- Treatment with rhEPO or CEPO does not further increase the FXN mRNA expression but the protein expression of cytosolic frataxin precursor protein after TRI.
- Previous studies reported that FXN protein expression is up-regulated in vitro after rhEPO or CEPO treatment (2,3). We show here for the first time that FXN precursor protein expression is increased after rhEPO and CEPO treatment in vivo.
- Results from this study support the notion that FXN is involved in EPO- and EPO analogues-mediated neuroprotection in vivo.

References