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Abstract

Erythropoietin (EPO), a hematopoietic cytokine, is produced primarily by interstitial fibroblasts in the adult kidney and by fetal hepatocytes. Interest in erythropoietin as a neuroprotective mediator has grown since it was found that systemically administered EPO is protective in several animal models of disease. However, given that the blood–brain barrier limits EPO entry into the brain, alternative approaches that induce endogenous EPO production in the brain may be more effective clinically and associated with fewer untoward side-effects. Astrocytes are the main source of EPO in the central nervous system. In the present study we investigated the effect of the inflammatory cytokine tumor necrosis factor a (TNFα) on hypoxia-induced upregulation of EPO in rat brain. Hypoxia significantly increased EPO mRNA expression in the brain and kidney, and this increase was suppressed by TNFα in vivo. In cultured astrocytes exposed to hypoxic conditions for 6 and 12 h, TNFα suppressed the hypoxia-induced increase in EPO mRNA expression in a concentration-dependent manner. TNFα inhibition of hypoxia-induced EPO expression was mediated primarily by hypoxia-inducible factor (HIF)-2α rather than HIF-1α. The effects of TNFα in reducing hypoxia-induced upregulation of EPO mRNA expression probably involve destabilization of HIF-2α, which is regulated by the nuclear factor (NF)-κB signaling pathway. TNFα treatment attenuated the protective effects of astrocytes on neurons under hypoxic conditions via EPO signaling. The effective blockade of TNFα signaling may contribute to the maintenance of the neuroprotective effects of EPO even under hypoxic conditions with an inflammatory response.