Chapter 22

NON-ERYTHROID FUNCTIONS OF ERYTHROPOIETIN

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Abstract: The oxygen-dependent, renal cytokine erythropoietin (Epo) is well known to increase red cell production. Binding of Epo to the Epo receptor (EpoR) represses apoptosis of erythroid progenitor cells, thereby allowing their final maturation. We and others showed that Epo and its receptor are expressed in many other tissues, including brain, spinal cord, retina and testis. The presence of a blood barrier suggests that Epo plays a local role in these organs. Indeed, therapeutically applied or hypoxically induced Epo has been shown to reduce the infarct volume in various stroke animal models, to prevent retinal degeneration, and to ameliorate spinal cord injury. In a study conducted by Ehrenreich and colleagues, stroke patients treated with Epo showed reduced infarct volume, fast neurological recovery and improved clinical outcome. In analogy to its function on erythroid progenitor cells, this neuroprotective effect of Epo might be explained by repression of programmed cell death. Apart from neuroprotection, there is an assumption that Epo present in breast milk has the potential to protect against mother-to-infant transmission of HIV. When using Epo at high doses for longer time periods; however, care has to be taken to control the resulting chronic polycythemia that most probably caused enlarged cerebral infarct volumes in a transgenic mouse model that due to Epo-overexpression reached hematocrit levels of about 0.8. Overall, these data strongly support the notion that Epo will soon find new applications in the clinic.

Key Words: neuroprotection, stroke, retinopathy, spinal cord injury, HIV

EPO AND ITS RECEPTOR ARE EXPRESSED IN THE MAMMALIAN BRAIN

Until recently, Epo gene expression was thought to be restricted to fetal liver and adult kidney (18). Binding of Epo to its receptor present on erythroid progenitor cells was shown to repress programmed cell death, thereby allowing their final maturation (24). However,
we and others discovered expression of Epo mRNA in other organs including brain, testis and lung (11, 25, 29, 42). In analogy to the kidney, Epo gene expression was regulated in an oxygen-dependent manner as observed in hypoxic monkeys (29) and mice (11). The presence of the blood-brain-barrier (BBB) excluded a systemic erythropoietic function of brain-derived Epo but suggested a local role of Epo in the brain by binding to local EpoR. Of note, Epo and its receptor were both expressed by neurons and astrocytes (1, 2, 29-31, 33, 34, 40). Interestingly, Epo gene expression in kidney and brain is different, suggesting a tissue-specific regulation: while hypoxia-induced expression of renal Epo peaked at 8h despite continuous exposure of mice to reduced oxygenation, cerebral Epo mRNA levels remained elevated for more than 24h (8). This tissue-specific regulation of Epo gene expression might be the result of the differential modulation of the hypoxic-inducible factor-1 (HIF-1), the key regulator of oxygen-dependent genes such as Epo (17). We have recently shown that the HIF-1-α subunit of this heterodimeric transcription factor peaked in the kidney after 1 h of hypoxic exposure followed by a marked decrease within 8 h despite continuous hypoxia. In contrast, HIF-1α level in the brain reached a plateau after 5h of hypoxia that was maintained for at least 24h (41).

EPO PROTECTS AGAINST BRAIN INJURY IN ANIMAL MODELS

Back in 1998, Sasaki and co-workers reported for the first time that Epo protects neurons from ischemic damage in vivo. By occlusion of the common carotid arteries, a model of global ischemia, followed by infusion of Epo into the lateral ventricles of gerbils, the authors observed a reduction of lethal ischemic damage of hippocampal CA1 neurons (37). This protection was reversed by infusing soluble EpoR that prevented Epo from binding to the endogenous EpoR in neuronal cells. The neuroprotective effect of intraventricular injected Epo was confirmed by further studies using rodent models with permanent occlusion of the middle cerebral artery (2, 3, 5, 36), reviewed in (27, 38). Of clinical interest was the fact that intraperitoneally given Epo exerted its neuroprotective function even when applied 6 h after middle cerebral artery occlusion in mice (3).

What are the mechanisms leading to Epo-dependent neuroprotection? Evidence accumulates that, by analogy to the situation during maturation of erythroid progenitor cells to erythrocytes (24), Epo might directly reduce cerebral apoptosis in the ischemic brain, most probably by activating anit-apoptotic genes such as bcl-2 and bcl-xL, or by inhibiting expression of apoptotic genes such as caspasases (39). Moreover, Epo has been reported to repress exocytosis of glutamate thereby preventing excitotoxic neuronal death (22). Further putative mechanisms are reviewed in Marti and Bernaudin (26).

DOES EPO CROSS THE BLOOD-BRAIN BARRIER (BBB)?

Originally, we and others did not observe any correlation between plasma Epo levels and Epo concentration in the cerebrospinal fluid obtained from patients with an intact BBB (28), even after intravenous injections of 6,000 IU Epo (4). In patients suffering from brain trauma, however, we observed a correlation of Epo levels with the severity of BBB dys-