Chapter 2

EXPRESSION OF ERYTHROPOIETIN AND ITS RECEPTOR IN THE CENTRAL NERVOUS SYSTEM

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Abstract: Erythropoietin (EPO) is a glycoprotein that is produced mainly by interstitial fibroblasts in the kidney. Released into the circulation, EPO makes its way to the bone marrow where it regulates red cell production by preventing apoptosis of erythroid progenitor cells. Recently, EPO has emerged as a multifunctional growth factor that plays a significant role in the nervous system. Both EPO and its receptor are expressed throughout the brain in glial cells, neurons and endothelial cells. Brain-derived EPO is upregulated by hypoxia, and expression of both EPO and its receptor are specifically modulated during cerebral ischemia. EPO has potent neuroprotective properties in vivo and in vitro and appears to act in a dual way by directly protecting neurons from ischemic damage and by stimulating endothelial cells, and thus supporting the growth of new blood vessels. EPO eventually also modulates inflammatory responses. Thus, hypoxically upregulated EPO is a naturally self-regulated physiological protective mechanism in the mammalian brain, especially during ischemia. As EPO is also a clinically extremely well studied and tolerated compound, its use in stroke patients is tempting.

Key words: neuron; astrocyte; microglia; endothelial cell; HIF-1; VEGF; IGF-1; angiogenesis; neuroprotection; apoptosis; hypoxia; ischemia; stroke.

1. INTRODUCTION

Clinicians, who are treating patients suffering from the anemia of End-Stage Renal Failure with recombinant erythropoietin (EPO), have often reported an improvement of the cognitive function of their patients (reviewed by Ehrenreich and Siren, 2001a). However, it was never quite
clear if this enhancement of cognitive function is the result of an increase in the oxygen transport capacity of the blood leading to an improved oxygenation of the brain, or if EPO has a direct effect on brain cells by itself. This latter assumption was largely disregarded because EPO was not thought to cross the blood-brain barrier, due to its large size (30 kDa) and its many negative charges (Davis et al., 1987; Recny et al., 1987). Indeed, results from various studies indicated that endogenous kidney-derived EPO only gets access into the brain after breakdown of the blood-brain barrier (Marti et al., 1997; Buemi et al., 2000). Nonetheless, recent evidence suggests that high amounts of recombinant EPO can attain the brain in a number of experimental settings (Brines et al., 2000; Juul et al., 2004), a finding that may explain the beneficial effects on cognitive function seen in these patients.

These observations led to two interesting questions that concern the presence of EPO and EPO receptors in the brain. First, as EPO mediates its effects through binding to its cognate receptor, EPO receptor should be expressed at the site of action in the central nervous system (CNS) to enable EPO to elicit biological functions. Second, if EPO receptors are naturally occurring in the CNS, one has to postulate that EPO is endogenously produced in the brain itself to activate these receptors, on the assumption that kidney-derived EPO does not cross the blood-brain barrier under physiological conditions. Indeed, it was demonstrated that EPO receptors are widely distributed in the mammalian brain, and that the expression of EPO mRNA and EPO protein largely coincides with the occurrence of EPO receptor mRNA and protein (reviewed by Marti and Bernaudin, 2003; Genc et al., 2004; Marti, 2004). The upregulation of brain EPO in a large number of experimental conditions associated with tissue hypoxia is well documented, and comprise many mammalian species including mice, rats, monkeys, and humans (Marti et al., 1996; Marti et al., 2000; Siren et al., 2001; Genc et al., 2004).

In this chapter we will first deal with the normal pO2 gradients within the brain. We will next consider those areas of the CNS that produce EPO and carry EPO receptors, and will finally have a look at the physiology of EPO function in the CNS, as an actor on neurons, glial cells and endothelial cells, including the action of EPO on the architecture of brain vessels.

2. OXYGEN GRADIENTS WITHIN THE BRAIN AND EXPRESSION OF HIF-1α AND HIF-2 α

The brain exhibits a high rate of oxygen consumption, comprising some 20% of the normal oxygen consumption at rest. Within the brain, the pO2