Editor’s Perspective

Preserving Brain Function During Development and Aging with Erythropoietin

Cognitive impairment can occur at any stage of life and results in a significant challenge in attempts to reverse or prevent the progression of mental impairment. Erythropoietin (EPO) is one agent that may offer new hope for the treatment of cognitive loss with the onset of neurodegenerative disorders. The EPO gene exists on chromosome 7 and represents a single copy in a 5.4 kb region of the genomic DNA. Ultimately, this gene encodes for a polypeptide chain that has initially 193 amino acids [1]. EPO is then processed as a protein and cleaved of a 27 amino acid hydrophobic secretory leader at the amino-terminal to result in a 166 amino acid peptide [2]. The processed protein is subsequently formed with the removal of a carboxy-terminal arginine in the mature human and recombinant human EPO (rhEPO) to lead to a circulatory EPO protein of 165 amino acids with a molecular weight of 30.4 kDa.

Erythropoiesis-stimulating agents that also include EPO are currently approved for the treatment of anemia that can occur from chronic kidney failure, human immunodeficiency virus, and chemotherapy. These agents also can be used to reduce blood transfusions for surgery. The primary site for the production and secretion of EPO are the kidney peritubular interstitial cells but EPO also is present in other organs that include the brain, liver, and uterus. EPO expression is regulated by changes in oxygen tension and not by the concentration of red blood cells as previously believed. However, it should be noted that EPO also is regulated through pathways that may not rely upon exposure to hypoxia. Hypoxia-inducible factor 1 (HIF-1) modulates the expression of EPO and the EPO receptor (EPOR) to increase the production of EPO. After HIF-1 is activated, the gene transcription of EPO and EPOR progresses and is controlled through the transcription enhancer region in the 3’-flanking region of the EPO gene that binds to HIF-1 [3, 4].

EPO functions through multiple signaling pathways that can lead to cellular protection and prevent apoptotic demise of cells. Phosphoinositide 3-kinase (PI 3-K) and protein kinase B (Akt) are considered primary pathways that offer cellular protection through EPO. EPO also oversees mammalian forhead transcription factors of the O class (FOXO), the silent mating type information regulation 2 homolog 1 (S. cerevisiae) (SIRT1), Wnt (wingless) proteins, and the mechanistic target of rapamycin (mTOR). Each of these pathways through EPO can have a significant impact on cellular development, differentiation, and longevity.

Recent studies are examining the role of EPO on preserving brain and cognitive function. For example, EPO is being considered for the treatment of Alzheimer’s disease [5]. Challenges exist for this therapy since EPO cannot cross the intact blood brain barrier, but activation of downstream signal transduction pathways for EPO may overcome these difficulties. EPO also may have utility in treating patients with ischemic stroke [6], but current work appears to be at an early stage since clinical outcomes can be variable and not directly correlate with experimental animal studies. Closely tied to dementia and cognitive loss is the progression of diabetes mellitus. New work has identified three EPO genetic variants that were significantly associated with mortality in patients. The results provide evidence that the EPO gene may be an independent predictor of mortality in patients with type 2 diabetes mellitus [7]. In regards to identifying a possible mechanism that EPO oversees during cognitive decline and hypoxia, EPO in experimental models was found to rescue synaptic proteins in the cortex and...
hippocampus and increase axonal density following exposure to hypoxia [8]. As a result, EPO may assist with synaptogenesis and neurite repair.

In this issue of *Current Neurovascular Research*, new work suggests that specific EPO gene polymorphisms are associated with a reduced susceptibility to brain injury in preterm infants. Through the examination of preterm infants with brain injury, *EPO* polymorphism rs551238 demonstrated an important difference in the genotypic distributions between the brain injury group and was significantly correlated with reduced susceptibility to brain injury in preterm infants. This *EPO* polymorphism may serve as a potential marker for brain injury prediction in preterm infants. Other work in this issue of *Current Neurovascular Research* examines the role of the blood brain barrier that can impact drug delivery to the brain, including EPO. At the cellular level, it appears that radial glia and endothelial cells are essential to promote vascular maturation and astrocyte generation for the blood brain barrier. Furthermore, in another study, loss of blood brain integrity may not only lead to gray matter injury, but also the loss of white matter in the nervous system. Other work in this issue elucidates the role of microRNAs during cognitive impairment, epilepsy, and spinal cord injury, immune activation that can alter mood and lead to depression, gender differences during hemorrhagic stroke, cystatin C during thrombolysis, and the role of vitamin D during ischemic injury and axonal regeneration. The novel studies in this issue of *Current Neurovascular Research* help us better define the potential role of novel therapeutic strategies such as EPO and look more in-depth to the multiple underlying biological pathways that must be addressed to offer new strategies for the preservation of brain function and cognitive well-being.

**REFERENCES**