EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 8
562-564
Year: 2016

ERYTHROPOIETIN AND RESPIRATORY RHYTHMOGENESIS IN HIGH ALTITUDE STRESS

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Article Received on 21/06/2016 **Article Revised on 11/07/2016** **Article Accepted on 31/07/2016**

ABSTRACT
Erythropoietin (Epo) is a glycoprotein that increases the production of red blood cells upon conditions of decreased oxygen availability. Epo not only increases the synthesis of erythropoietin but also due to its expression in the brain it may have multiple physiological roles as a critical component of pulmonary renal cascade and in particular in respiration under stressful conditions. In rodents the Epo increases hypoxic ventilator response and may be involved in respiratory rhythmogenesis. This review examines the importance of Epo in stressful respiratory situations like for e.g the high altitude stress.

KEYWORDS: Erythropoietin, respiration, stress, altitude, erythrocytes.

INTRODUCTION
Epo binds with the human haematopoietic Epo receptor which is a 484 amino acid glycoprotein of about 60 kDa, which belongs to the cytokine class I receptor family and forms homodimers. On this binding of Epo to the Epo-R dimer, cytoplasmic Janus kinases 2 (JAK2) catalyses the phosphorylation of tyrosine residues of the Epo-R and of various intracellular proteins that includes enzymes and transcription factors. Erythropoietin thus mediates its key signal transduction actions through the tyrosine kinase modulation. Erythropoiesis is a slow-acting process.[1] Following a rise in plasma Epo it takes 3–4 days before reticulocytosis becomes apparent. Epo is thus essential for erythropoiesis. But the action of Epo is augmented by several other hormones, namely thyroxine, somatotropin and insulin-like growth factor 1. The higher RBC counts and haemoglobin concentrations in men compared to women result from the stimulation of erythropoiesis by androgens and its inhibition by oestrogens. Most of the present knowledge of the O_2-sensing mechanism in control of Epo production has been based on *in vitro* studies utilising human hepatoma cells lines Hep3B and HepG2. It is noteworthy, that the mechanisms of the renal and the hepatic *Epo* expression differ. (a) Renal cells respond in an all-or-nothing fashion to hypoxia[2], whereas hepatoma cells respond in a graded way (b). The hypoxia-response elements (HREs) in control of the *Epo* gene are located upstream in the kidney (between 9.5 and 14 kb 5′ to *Epo*) but downstream in the liver (within 0.7 kb 3′ to *Epo*) according to studies conducted in transgenic mice.[3] In both tissues *Epo* expression is under the control of distinct transcription factors. The *Epo* promoter is suppressed by GATA-2 in normoxia.[4] GATA-2 levels decrease in hypoxia.[5] More importantly, the *Epo* enhancer is activated by hypoxia-inducible transcription factors (HIFs). These are composed of an O_2-labile α-subunit (120 kDa; isoforms 1α, 2α or 3α) and a constitutive β-subunit (90–95 kDa). Although the prototype HIF-1 was discovered in studies of *Epo*.[6]

Epo receptor and high altitude stress
The Plasma sEpoR has been suggested to increase as Epo level falls until both reach a new steady state. Despite the short duration of hypoxic exposure used in these studies, the evidence of a dynamic interplay between Epo and sEpoR provides evidence that the latter might be part of a fine-tuned mechanism that regulates Epo availability and, therefore, the stimulation of erythropoiesis.[7] This mechanism is similar to that reported for other soluble cytokine and growth factor receptors generated by alternative mRNA splicing. In this regard, the effects of the cytokine interleukin-4, is a good example and shows that it is positively regulated by its membrane-bound receptor and negatively by the soluble receptor protein. Another example includes the soluble epidermal growth factor receptor, which acts as an antagonist and competes with the membrane receptor for binding its ligand epidermal growth factor. The fact that sEpoR levels show a decrease with hypoxic exposure suggests that EpoR mRNA splicing machinery is hypoxic sensitive.[8,9] Modifications on alternative splicing of several genes have been reported as a physiological response to hypoxia, whether by upregulating or downregulating splice isoform expression. Thus it is possible that chronic

hypoxemia is associated with long-term alteration of EpoR mRNA splicing, which leads to the down regulation of the sEpo receptor protein. This was the first study to report the pattern of Epo and sEpoR in healthy Andean highlanders and in highlanders with EE with normal and high plasma Epo concentration. The existence of three subgroups of highlanders (healthy, normal-Epo CMS and high-Epo CMS) suggests a differential regulation of Epo and sEpoR and a physiological role of sEpoR in the modulation of the erythropoietic stimulus. Moreover, the physiological differences in the Epo system among the groups and their erythropoietic response might indicate specific underlying genetic backgrounds, which might, in turn, reflect different levels of adaptation to lifelong high-altitude hypoxia.[10]

Epo and influence on respiratory rythmogenesis

EPO and EPOR are highly expressed in the developing central nervous system. In contrast, their expression is markedly reduced postnatally and remains low in the normal adult brain. This author had suggested that erythropoietin is a critical component of the 'pulmonary renal cascade' and was involved in maintaining respiration particularly during stressful conditions like the high altitutde respiratory stress and deep water stress on respiration. This could be due to the release of erythropoietin from the kidney into blood circulation and subsequent effects on central respiratory centres in the midbrain area and also in the lungs. There is now evidence that erythropoietin is expressed in discrete sites of the brain and may be involved in respiratory resuscitation and physiological adaptation to respiratory stress.[11]

Epo and erythropoiesis and hypoxia inducible factor

In the EPO and EPOR circuits, important new components are now being revealed. Several of these regulate endogenous EPO expression. The Apo-IRP1 is known to inhibit Hif2a transcript translation, whereas on the other hand the iron reverses this effect, thereby enhancing HIF2a and EPO levels [12]. Pharmacologically, the prolyl 4-hydroxylases (PHD) inhibitors that stabilize HIF2a can likewise increase EPO expression, as does acetate supplementation which causes the Hif2a acetylation during stress erythropoiesis [13]. Thus hypoxic stress could enhance the synthesis and release of Epo.

Effect of high altitude on physiological parameters

In humans high altitude illness occurs in those subjects who travel too high and at rapid pace, and it presents with headache, nausea, anorexia, fatigue, lassitude, and sometimes even death. Increased oxidative stress and reduced antioxidant defense have been observed in animals, with exposure to a simulated milieu of high altitude.[14] In addition, localized free radical generation caused by skeletal muscle damage may also cause vascular damage of the blood-brain barrier and contribute to the patho-physiology of acute mountain sickness. Furthermore, the erythropoietin response to hypoxia was increased by altitude acclimatization.

Signal transduction by Epo

Structural analysis suggested that unliganded EPO-R exists as a preformed homodimer in an open scissor-like conformation and that dimerization induced by the transmembrane domain keeps the unliganded EPO-R in an inactive state. Physiologic amounts of EPO, by binding to the receptor, can then switch the receptor to an activated state.[15] A central signaling pathway activated by the EPO-R requires the participation of JAK2. EPO-mediated receptor dimerization brings two receptor-associated JAK2 molecules into close proximity. This enables them to transphosphorylate and activate each other, after prior phosphorylation of some or all of the eight Tyr residues in the intracellular domain of EPO-R. Gene targeting studies have demonstrated that JAK2 plays a pivotal role in signal transduction via cytokine receptors, which are required for definitive erythropoiesis.[16] Tyr phosphorylation of STAT proteins (signal transducers and activators of transcription) precedes JAK2 activation and links growth factor receptors to gene transcription.[17]

Erythropoietin in respiration and possible role in rythmogenesis during stressful conditions

Several studies suggest that Epo modulates the central respiratory drive and a interesting study by Ursula von Wussow[18] has shown the importance of brain respiratory centres in the release of Epo. This author had suggested in 2004 about the existence of the pulmonary renal cascade and the importance of Epo in this cascade. Experimental studies suggest that Epo increases the hypoxic ventilator response under conditions of severe hypoxia (6% of O_2). Epo seems to directly act on the central nervous system to modulate the translation of the inputs from peripheral chemoreceptors to respiratory network in the medulla. In mice it has been shown that Epo receptor changes the response to hypoxia, suggesting that endogenous synthesis of Epo might stimulate respiration, at least in response to hypoxia.

CONCLUSION

The plethora of experimental data on Epo supports the contention of this author that Epo contributes to the maintenance and possible rythmogenesis of respiration. It appears that brain centres contribute to the release of Epo from the kidney during respiratory stressful conditions like the high altitude stress and possible also during decompression while diving under in deep water. Thus it is becoming clear that Epo may contribute even in respiratory ryhthmogenesis during stressful conditions and thus may play multiple roles in patho-physiology and homeostasis in humans and other mammals.

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