Biomedicine & Pharmacotherapy 105 (2018) 956–961

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Erythropoietin: A potential drug in the management of diabetic neuropathy

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ARTICLE INFO

Keywords:
Erythropoietin
Diabetic neuropathy
Oxidative stress
Inflammation
Apoptosis

ABSTRACT

Erythropoietin (EPO) is required for promoting the progress of erythroid differentiation. However, the discovery of EPO and the EPO receptor (EPOR) in the nervous system may contribute to new treatment strategies for the use of EPO in neurodegenerative disorders. Diabetic neuropathy is a neurodegenerative disease that affects a large proportion of diabetic patients and results in alterations in functionality, mood and sleep. The pathogenic mechanisms generating diabetic neuropathy involve: Schwannopathy, polyol pathway activity, advanced glycation end-products (AGEs) accumulation, protein kinase C (PKC) activity, increased hexosamine pathway flux, oxidative stress, nitric oxide and inflammation. In this sense, evidence from both clinical and experimental studies indicates that EPO may reverse diabetic neuropathy through an antioxidant action by decreasing pro-inflammatory cytokines, restoring Na+/K+-ATPase activity, and blocking the generation of pro-apoptotic proteins. The aim of this review is to discuss the neuroprotector effect of EPO on pathogenic mechanisms of diabetic neuropathy.

1. Introduction

Diabetic neuropathy is the most common complication in types 1 and 2 diabetic patients. It is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in diabetic patients after the exclusion of other causes [1]. Clinical symptoms of diabetic neuropathy can be divided into positive and negative types depending on which nerve fibers are affected [2]. Patients who present positive symptoms develop abnormal sensations, frequently allodynia (painful sensations to innocuous stimuli) and hyperalgesia (increased sensitivity to painful stimuli), whereas patients with negative symptoms can experience sensory loss leading to feet ulceration and amputation [3]. Some diabetic patients suffer pain and sensory loss at the same time [4].

Erythropoietin (EPO) is a glycoprotein hormone, known for its erythropoietic activity, and used as treatment for anemia in humans with renal failure or cancer. In addition, EPO reduces the amount of blood transfusions required on premature infants and surgeries [5,6]. Several data suggest that EPO has other biological functions including neuroprotection in neurodegenerative diseases such as Alzheimer's, Parkinson's and depression [7–10]. Similarly, the use of EPO may be a potential therapeutic strategy to reverse diabetic neuropathy [11]. Therefore, the aim of this review is to analyze EPO as neuroprotective agent in diabetic neuropathy.

2. Erythropoietin biological function

EPO is an active protein constituted of 165 amino acids and molecular weight of 30.4 kDa. EPO has a high carbohydrate content distributed in 4 different loci: three N-linked glycosylations bound to asparagine residues at positions 24, 38, and 83, and one O-linked glycosylation bound to a serine residue at position 126. The O-linked carbohydrate chain consists of Gal-GalNAc and sialic acid, whereas the N-linked site is formed of a tetra-antennary structure with N-GlcNAc and sialic acid adhered to a mannose cluster [12,13]. The oligosaccharide chains are responsible for EPO production, secretion, longevity, and functioning and the sialic acid at the end of some carbohydrate chains of EPO intervenes in its metabolism and plasma half-life. The biological activity of EPO depends upon two disulfide bonds, one formed between cysteine7 and cysteine160, and the other between cysteine29 and cysteine33 [12,13].

HIF-1(hypoxia-inducible factor 1) is a transcription factor activated under hypoxic conditions. This factor increases the transcription and expression of EPO, as well as those of the EPO receptor (EPOR) to compensate for oxygen decrease [14]. EPO gene transcription is

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https://doi.org/10.1016/j.biopha.2018.06.068
Received 25 April 2018; Received in revised form 6 June 2018; Accepted 13 June 2018

mediated by the transcription enhancer located at the 3′-flanking region of the EPO gene, which specifically binds to HIF-1. EPO is produced and secreted in the liver during fetal development; in adulthood it is produced and secreted by kidney peritubular cells. This protein acts by binding to EPOR expressed during the erythroid colony-forming unit (UFC-E) and pro-erythroblast stages, as a protection against apoptosis [15]. Protection activity induces cell proliferation and maturation from normoblasts to reticulocytes, which in turn are released from bone marrow into blood circulation via erythrocytes. This action helps increase oxygen under hypoxia conditions [16]. Apart from the kidneys, other organs (brain, retina, reproductive tract, skeletal muscle myoblasts and insulin-producing cells) have been identified as EPO producers and secretors [17]. For instance, uterus EPO production is stimulated by estrogens (17β-estradiol), which increase proliferation of uterine endometrium during hypoxia [18]. It is known that hippocampus, internal capsule, cortex, midbrain, endothelial cells and astrocytes also synthesize EPO under hypoxic conditions [19].

On the other hand, EPOR is expressed in non-hematopoietic tissues (endothelial, retinal, lung, liver, myocardium, adipocytes, macrophages and pancreatic cells); also, in central (hypothalamus, hippocampus and neocortex, and spinal cord) and peripheral (dorsal root ganglia, nerve axons, and Schwann cells) nervous systems [16,20]. Several studies suggest that other stimuli (hypoglycemia, increased intracellular Ca2+, neuronal depolarization, and reactive oxygen species) enhance EPO expression through the activation of HIF. Alternately, anemic stress, insulin release, tumor necrosis factor α (TNF- α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) also stimulate EPO and EPOR expression by HIF-independent pathways [21,22]. In non-hematopoietic tissues, the expression of EPO and EPOR is a pleiotropic biological function (proliferation, protective/survival activity, maintenance, or repair).

In patients with chronic renal failure (trauma, chemotherapy, kidney transplants) EPO concentrations decrease and anemia is induced. To treat this condition, a pharmacological alternative is to administer recombinant human EPO (rhEPO). However, diverse reports have shown that long-term treatments with rhEPO induce adverse effects (hypertension, convulsions, thrombotic events, polycythemia, and red cell aplasia); it is also possible to develop cellular progression and in consequence tumor generation [23].

2.1. EPO-EPOR interaction induces intracellular signaling pathways

EPOR, a transmembrane receptor, is member of the type I cytokine superfamily. This receptor has two subunits and its molecular weight is 66 kDa [24]. EPOR in non-hematopoietic tissues is associated with the β-common receptor subunit (EPOR-βcR). It is known that the interleukin-3 receptor (IL-3R) and the granulocyte macrophage colony-stimulating factor receptor (GM-SCFR) are linked to the β-common receptor subunit. Interestingly, EPOR-βcR is involved in EPO-induced neuroprotective activity [25,26].

EPO/EPOR interaction also has signaling pathways in neuronal and non-neuronal systems by the phosphorylation of protein Janus kinase 2 (JAK2), which is attached to EPOR at the transmembrane domain. The activation of JAK2 induces multiple signaling pathways including the signal transducer and activator of transcription 5 (STAT5), phosphoinositide 3-kinase (PI3K/Akt), p42/44 mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) [27–29]. JAK2-induced by EPOR phosphorylation, allows STAT5 phosphorylation and dimerization. Subsequently, STAT5 translocates to the nucleus and leads to the transcription of anti-apoptotic proteins such as Bcl-xL and Bcl-2 [30].

EPO-mediated PI3K/Akt leads to Akt phosphorylation (serine473). The activation of PI3K/Akt deactivates Bad, the pro-apoptotic protein [31]. EPO-Akt prevents cellular apoptosis by FoxO3a phosphorylation, thus preventing nuclear translocation and transcription of pro-apoptotic genes [32,33]. Moreover, EPO-Akt activates the mammalian target of rapamycin (mTOR) and together with the phosphorylation of p70 ribosomal S6 kinase (p70S6K) elicit the expression of anti-apoptotic Bcl-2/Bcl-xL and Bad inactivation, causing the expression of anti-apoptotic genes Other reports indicate that Wingless (Wnt) pathways are associated with Akt, FoxOa3 and mTOR. In particular, EPO-Wnt1 induces the phosphorylation of Akt and glycogen synthase kinase-3β (GSK-3β) that promote the translocation of β-catenin to the nucleus, starts the transcription of anti-apoptotic genes and inhibits the transcription of pro-apoptotic genes. Moreover, Wnt1 regulates XIAP, the X-linked inhibitor of the apoptosis protein, and the apoptotic protease activating factor 1 (Apaf-1); these processes prevent the activation of caspases [34,35]. Otherwise, NF-kB belongs to the REL family of proteins; this protein can be present as homodimer or heterodimer and it contains the sub-units p65, p50, p52, RelB and c-Rel [56]. NF-κB is activated by phosphorylation of IκB, the κB inhibitor. As a result, IκB releases the p50 subunit, which subsequently translocates to the nucleus and initiates the transcription of anti-apoptotic proteins [36].

2.2. Pleiotropic effects of EPO

EPO promotes endothelial nitric oxide synthase (eNOS) activation associated with PI3K/Akt signaling. It contributes to cardiac mitochondrial biogenesis by enhancing peroxisome proliferator-activated receptor gamma (PPAR-$^{\gamma}$) and co-activator 1 (PGC-1α), as well as increasing the number of mitochondria. Therefore, EPO is considered a cardio-protector [37]. In an ischemia/reperfusion model in rats, EPO enhances EPOR activation and this in turn activates the PI3K/Akt pathway, which inhibits the inflammatory response mediated by NF-kB in intestine. As a result, intestine protection is generated against the ischemia/reperfusion injury [38]. Moreover, EPO treatment provides protection against insulin produced in pancreatic B-cells via anti-apoptotic, anti-inflammatory, and angiogenic effects in db/db mice and in streptozotocin-induced diabetic mice [39]. A recent report suggests that EPO enhances obesity and glucose homeostasis in obese mice, inducing brown adipocyte differentiation and thermogenesis, as well as reduction of gluconeogenesis-related genes in liver [40].

On the other hand, EPO exerts its neuroprotective effect against hypoxia, ischemic brain injury, glutamate exposure and Aβ toxicity, and inflammation. Different studies have reported that the activation of PI3K/Akt pathways protects dorsal root ganglion neurons and retinal cells in diabetes [41,42]. EPO, through Wnt1, leads the inactivation of FoxO3a and maintains cerebral endothelial survival during experimental diabetes [43]. Other studies suggest that mTOR and p70S6K activation exert a neuroprotective effect of EPO against sepsis, as well as protection during exposure to oxygen-glucose deprivation [44]. EPO activates Wnt pathways to limit tubular cell apoptosis during renal ischemia/reperfusion and thus maintains the survival of mesenchymal stem cells under hypoxia, glutamate exposure and Aβ toxicity [45,46]. Besides, EPO enhances the protection of mesenchymal stem cells on diabetic rat-derived Schwann cells by increasing GSH levels, up-regulation of p-Akt and Bcl-2, and down-regulation of caspase-3 and Bax [47,48]. These signaling pathways may play an important role as neuroprotectors in diabetic neuropathy. However, the information of EPO-mediated signaling pathways in diabetic neuropathy is limited.

3. Diabetic neuropathy

In the peripheral nervous system, the majority of glucose is absorbed by Schwann cells (SCs) and in less proportion by neurons via insulin-independent glucose transporters (GLUTs) [49,50]. Therefore, it has been proposed that SCs generate lactate, which is later transported to the axon by monocarboxylate transporter, here lactate is used as energy source to maintain nerve integrity. Schwannopathy due to hyperglycemia may result in low amounts of glial lactate and decreased production of pyruvate in the axon. Moreover, the axonal glycolytic intermediates, which participate in the pathogenic pathways, such as polyol, advanced glycation end-products (AGEs), activation of protein kinase C (PKC) and hexosamine contribute to pyruvate decrease. The