The influence of the pleiotropic action of erythropoietin and its derivatives on nephroprotection

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Erythropoietin (EPO) is traditionally described as a hematopoietic cytokine or growth hormone regulating proliferation, differentiation, and survival of erythroid progenitors. The use of EPO in patients with chronic kidney disease (CKD) was a milestone achievement in the treatment of anemia. However, EPO involves some degree of risk, which increases with increasing hemoglobin levels. A growing number of studies have assessed the renoprotective effects of EPO in acute kidney injury (AKI) or CKD. Analysis of the biological effects of erythropoietin and pathophysiology of CKD in these studies suggests that treatment with erythropoiesis-stimulating agents (ESAs) may exert renoprotection by pleiotropic actions on several targets and directly or indirectly slow the progression of CKD. By reducing ischemia and oxidative stress or strengthening anti-apoptotic processes, EPO may prevent the development of interstitial fibrosis and the destruction of tubular cells. Furthermore, it could have a direct protective impact on the integrity of the interstitial capillary network through its effects on endothelial cells and promotion of vascular repair, or modulate inflammation response. Thus, it is biologically plausible to suggest that correcting anemia with ESAs could slow the progression of CKD.

The aim of this article is to discuss these possible renoprotection mechanisms and provide a comprehensive overview of erythropoietin and its derivatives.

Key words: erythropoietin • erythropoiesis-stimulating agents • nephroprotection • chronic kidney disease • anemia

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Background

The first reports of the existence of a factor stimulating blood formation were reported in 1906, when Carnot and DeFlandre discovered the substance in rabbit blood and called it hematopoietin [1]. However, the relationship between erythropoiesis and hypoxia were discovered a just few years earlier in 1893 by Meischer. In 1948, Bonsdorff and Jalavisto introduced the concept of erythropoietin and its effects closely linked to red blood cell synthesis [2]. The humoral nature of erythropoietin was documented in 1953 by Allan Erslev [3], who, 2 decades later, thanks to a new Northern blot technique, detected erythropoietin mRNA. The first human EPO was isolated from urine of patients with pernicious anemia in 1977, following successful isolation of the hormone from the serum of anemic sheep in 1962 by Goldwasser [4]. Two scholars, Lin and Jacobs, independently of each other, isolated and cloned the gene encoding erythropoietin in 1985 [5,6]. For the first time in humans, EPO was used in clinical trials in 1986 by Winearls and Eschbach [7,8].

Erythropoietin is a glycoprotein that is hydrophobic, heat-stable, and insensitive to pH changes. EPO is synthesized mainly by fibroblast-like cells in the human renal cortex and outer medulla (approximately 80–90% of total production) and in the liver (the remaining 10–20%) [9,10]. A small amount of EPO mRNA was demonstrated in lung, testis, spleen, vascular endothelial cells (mostly capillary), placenta, uterus, and brain of experimental animals subjected to hypoxia. EPO is a 193-amino acid glycoprotein, of which 27 N-terminal residues of a signal sequence allow the transport of newly synthesized protein across cell membranes. After proteolysis of the signal peptide, the new pro-peptide is formed with arginine located at the C-terminus. Mature EPO -165 amino acids glycoprotein is formed by the action of carboxypeptidase, which hydrolyzes the C-terminal arginine residue. The main factor governing the rate of EPO production in the kidney is the concentration of oxygen. The increase in EPO synthesis in response to hypoxia is regulated by hypoxia-inducible factors (HIFs) [11,12]. The rate of EPO secretion depends only on its synthesis rate, because there are no intracellular stores of this hormone. The EPO gene is located on chromosome 7 (locus 7q11-q22) and contains 4 key sequences. The kidney-inducible element (KIE), responsible for gene expression in the kidney, is located at the end of the 5′ sequence of the gene. The negative regulator element (NRE) is located closer to the transcription start site sequence (between 400 and 6000 base pair). The NRE is responsible for inhibition of EPO gene expression in organs that do not have the ability to synthesize EPO. EPO is composed of a polypeptide chain and 60% by weight of the molecule consists of 4 carbohydrate chains, which is accompanied by the presence of sialic acid residues (with a maximum number of 14 in the molecule) [13]. This structure determines secretion, half-life, and biological activity of EPO. Greater attached sialic acid-containing carbohydrate content of the molecule is associated with lower affinity for EPO-R, but a longer half-life and more effective stimulation of erythropoiesis [14].

There is no difference in sequence of amino acids between recombinant human EPO (rHuEPO) alpha and natural EPO synthesized in the human body. The exception may be darbepoetin alpha, which was engineered to contain 5 N-linked carbohydrate chains (2 more than in rHuEPO) and sialic acid residues for a total of 22. The effect of the changes was to extend operating time and increased biological activity in vivo. Therefore, the newly formed erythropoietin has less affinity for EPO-R and has an approximate 3-fold longer serum half-life, with greater in vivo potency [15]. In terms of chemical molecule, darbepoetin alfa differs from human EPO in primary structure. However, to designate the whole group of erythropoietic molecules, the term "erythropoiesis-stimulating agents" was introduced. Currently, the group of erythropoiesis-stimulating agents include: epoetin alpha (Eprex), epoetin beta (NeoRecormon), epoetin delta (Dynepo), darbepoetin alfa (Aranesp), and methoxy polyethylene glycol-epoetin beta (Mircera). The latter of these compounds is epoetin beta after chemical modification consisting in attaching, via amide bridges, to 30 kDa polypeptide chain methoxy polyethylene glycol molecules. Therefore, the newly formed substance is characterized by even longer duration of action than epoetin beta. Due to its properties, this molecule is also called continuous erythropoietin receptor activator (CERA) [16,17].

Current production of the new ESAs, known as biosimilar medicines, is the result of the expiration of patent protection for drugs produced by biotechnological methods in the pharmaceutical industry. An example is Binocrit, which after establishing bioequivalence to the original prototype Eprex has been registered by the European Medicines Agency (EMA) [18].

During the last decades, the biochemistry, physiology, and application of EPO have been studied extensively. Most of the studies have documented hematopoietic properties, including their safety and only a few non-hematopoietic abilities of EPO in a variety of tissue. The main indication of EPO in patients remains the same – to treat renal anemia and anemia associated with chemotherapy. However, non-hematopoietic properties of EPO and the wide-spread distribution of EPO-R on renal cells, endothelial, and vascular smooth muscle cells, cardiomyocytes, cardiac fibroblasts, mononuclear cells, gastric cells, retinal and prostate cells, human hair follicles, and auditory hair cells in the inner ear, as well as the central and peripheral nervous system [10,19–22], raised the possibility that EPO may exert broad protective actions on many targets, including nephroprotection.
Nephroprotection

Nephroprotection is any kind of activity including both non-pharmacological and pharmacological strategy for treatment that minimizes adverse effects, especially due to ischemia or oxidative stress on renal vasculature and renal cells or glomerular and interstitial inflammation with subsequent fibrosis or influence on apoptotic processes, which thereby contributes to progressive renal function loss. EPO-dependent protection may be due to direct impact of EPO on the kidney or indirectly through the impact on other organs and tissue by acting on different mechanisms mentioned above, which are jointly responsible for renal injury and progressive renal function loss.

Direct Mechanism of EPO Nephroprotection

The discovery of EPO-R in the kidney suggested that EPO may act directly in the autocrine-paracrine mechanism within the kidney mediates cytoprotection [23]. EPO-R is expressed by mesangial cells, proximal and distal tubular cells, and the collecting duct cells. The same EPO-R was also detected in kidney cancer cells and in cyst epithelia from polycystic kidneys [10]. The decrease in production of EPO by the kidneys affects both AKI and CKD. Scientific reports indicate that in ischemic AKI, renal synthesis of EPO is significantly decreased, whereas EPO-R level stay unchanged; thus, a cytoprotective effect may take place by administration of exogenous EPO [23]. Studies performed on animal models revealed a protective effect of EPO in the experimental setting of ischemic, septic, hemorrhagic, radio contrast media, and toxic cisplatin mechanisms of acute kidney injury [23]. In another study, the cytoprotective effect was achievable both 30 min and 6 h after ischemic kidney injury compared with the respective control group [24]. In all of the above-mentioned studies, EPO had no effect on Hb concentration within the time frame of the studies [23–26]. Thus the nephroprotection may occur at an early stage, without an increase in hemoglobin levels, which in turn proves that these mechanisms do not strictly depend on the hematopoietic properties of EPO-R.

However, a study in which investigators performed a double-blind placebo-controlled trial to assess whether early treatment (within 6 h of injury) with high doses of EPO (up to 50,000 U) could prevent the development of AKI in intensive care unit patients failed to demonstrate effectiveness. High doses of EPO did not alter the outcome of AKI in patients group receiving EPO compared with patients group receiving placebo. EPO did not cause EPO-related adverse events and early intervention with high doses of EPO was safe [27]. However, this study had a limitations – a composite of 2 biomarkers (the proximal tubular brush border enzymes gamma-glutamyl transpeptidase and alkaline phosphatase) was insufficient for risk stratification in a patient population with heterogeneous onset of AKI [28]. Therefore, a more precise application of biomarkers in different clinical settings of AKI could confirm earlier results obtained in animal models [29].

The nephroprotective effects of EPO in CKD patients have been poorly studied, perhaps because the therapeutic efforts in CKD patients were made only to correct anemia and the putative ischemic renal tissue damage as a result of anemia. Some results from recently published large trials in patients with CKD revealed no beneficial effect on progression CKD [30]. However, a study by Gouva et al., in which EPO therapy was started in CKD patients with only mild to moderate anemia to correct hemoglobin to subnormal levels over a period of 6 months, revealed a significant reduction of the progression of renal disease and delays the initiation of renal replacement therapy in the group of EPO-treated patients [31].

Indirect Mechanism of EPO Nephroprotection (Impact on Endothelium and Cardiovascular Function)

The best example of the indirect nephroprotection achieved by EPO is its impact on the cardiovascular system, where EPO treatment is associated with improved left ventricular ejection fraction [32]. Strengthening myocardial function, EPO increases renal perfusion in patients with chronic heart disease (CHD) and anemia. Moreover, EPO treatment is responsible for reduction in left ventricular mass index (LVMI), which is associated with the increase in both all-causes and cardiovascular survival rate [33]. Patients with CKD are at increased risk of cardiovascular adverse events, particularly dialysis patients, whose mortality may be up to 100 times greater than for the general population [34]. Furthermore, EPO acting on endothelial progenitors, enhances reendothelialization via Akt-endothelial nitric oxide synthase activation and prevents neointimal hyperplasia [35]. Erythropoietin also improved skeletal muscle microcirculation through the activation of eNOS in an animal model [36].

However, EPO administration in patients with STEMI, treated with PCI, was not associated with reduction of the infarct size in contrast to higher rates of adverse cardiovascular events, particularly increased infarct size among older patients [37]. Some studies indicate that long-term administration of EPO may have the potential to affect plaque stability [38]. Statins in dialyzed patients demonstrate nephroprotection associated with lower inflammation and erythropoietin responsiveness index [39–41].

The Influence of EPO on Inflammation and Fibrosis

Chronic inflammatory processes frequently occur in patients with CKD; they are particularly more common in patients with
end-stage renal disease [41–43]. The presence of immune disorders is the result of uremic toxins and immune cell activation by dialyzer membranes in patients undergoing hemodialysis [44,45].

EPO therapy in hemodialysis patients restores the ratio of CD4+/CD8+ to the normal level, although at the expense of decrease in CD8+ cells and increase in CD4+. EPO directly affects B cells and increases the production of antibodies [46]. Increased production of antibodies is also indirectly dependent on increased activity of helper T lymphocytes.

Pro-inflammatory cytokines such as interferon-γ (IFN-γ), tumor necrosis factor α (TNF α), interleukin-1, and 6β (IL-1 and IL-6β) are responsible for inhibiting the synthesis of EPO, which was revealed in studies both in vitro and in vivo [47,48]. TNF α exerts its biological activity by signaling via its 2 receptors, TNFR-1 and TNFR-2, and by activating NF-kappaB, which is essential for survival of many cell types [49]. There more, the action of TNF α has both apoptotic and anti-apoptotic consequences due to altered balance between different cell signaling pathways [50]. Both TNF-α synthesis and TNF-α induction of apoptosis increase with human aging. Moreover, TNF-α and Fas are the main activators of extrinsic apoptosis pathway, which occurs through the activation of so-called “death receptors”, which are cell surface receptors that transmit apoptotic signals after ligation with specific ligands. Death receptors belong to the TNF-α receptor gene superfamily, including TNFR-1, Fas/CD95, and the TNF-related apoptosis-inducing ligand (TRAIL) receptors DR-4 and DR-5 [51]. IFN-γ, TNF-α, TRAIL, and IL-1β are cytokines responsible for the inhibition of proliferation and differentiation of erythrocytes progenitors. Therefore, anemia is partly due to the induction of apoptosis and inhibition of cell growth, and decreasing the amount of EPO-R is the result of the local action of cytokines and iron metabolism [52].

EPO modifies the cellular inflammation process by inhibiting the expression of pro-inflammatory cytokines IL-1 and TNF-α and decreased pro-inflammatory mediators such as osteopontin and C-reactive protein. One of the mechanism of EPO protection against TNF-α depends on NO derived from endothelial cells [53].

Low-dose darbepoetin alpha treatment significantly ameliorated acute tubular injury and interstitial inflammation through increasing the survival of tubular cells and contributed to preservation of peritubular capillaries and reduction of interstitial fibrosis in a mouse model of aristolochic acid nephropathy [54]. Vascular and tissue protection is associated with persistent stimulation of the pro-survival Akt signaling pathway by darbepoetin alpha [55]. Furthermore, EPO treatment is responsible for the decreased pro-fibrotic mediators (transforming growth factor-beta1 and transforming growth factor-beta1-inducible gene-h3), which cause fibrosis with subsequent progressive renal function loss [56].

The Influence of EPO on Oxidative Stress Injury

Oxidative stress is the result of the lack of balance between the generation of reactive oxygen species (ROS) and the existing antioxidative defense mechanisms. Oxidative stress plays an important role in the pathogenesis of many diseases, including tissue injury. ROS are responsible for destruction of mesangial cells by altering lipid metabolism, as observed in patients with glomerulonephritis and nephritic syndrome. Inactivation of nitric oxide by superoxide anion radical increases vascular resistance in renal arteries and contributes to the development of hypertensive nephropathy [57]. Oxidative stress is well documented as an important factor in the development and progression of diabetic nephropathy, which is one of the main causes of CKD [58]. Pro-inflammatory processes with subsequent activation of free radical processes play important roles in destruction of the kidney structure and in urinary system infections. Oxidative stress may also play a key role in the development and progression of chronic allograft nephropathy (CAN) [59].

Some studies have indicated that EPO may prevent the overproduction of reactive oxygen species in diabetes nephropathy [60,61]. Erythropoietin delta protects human renal tubular epithelial cells against oxidative stress by a dose-dependent inhibition of reactive oxygen species formation. This protective effect is possibly related to the membranous expression of the EPO-R. Oxidative stress reduction is associated with the upregulation of renoprotective genes such as heme oxygenase-1 (HO-1), aquaporin-1 (AQP-1), and B-cell CLL/lymphoma 2 (Bcl-2), carboxypeptidase M (CPM), and dipeptidyl peptidase IV (DPPIV) [61].

The Influence of EPO on Apoptosis

Erythropoietin molecule binding to EPO-R causes the homodimerization on EPO binding, followed by autophosphorylation of Janus tyrosine kinase-2 (JAK-2). JAK-2 activation leads to phosphorylation of several downstream signaling pathways, including Ras-mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI-3-K). Another important element in signal transduction by the JAK-2 is a signal transducer and activator of transcription 5 (STAT 5), which affects the activity of the genes Bcl-2 and Bcl-XL [11,62].

With the conversion of phosphatidylinositol dependent on PI-3-K and activation of serine/threonine kinase Akt, comes the
induction of Bcl2 family of proteins, which in turn are responsible for the inhibition of apoptosis – the cell death program triggered by activation of certain proteases (caspases). Proteins Bcl2 are displayed on the outer membranes of mitochondria in a healthy cell. Internal damage to the cell causes a protein, Bax, to migrate to the surface of the mitochondrion, where it inhibits the protective effect of Bcl-2 and inserts itself into the outer mitochondrial membrane, causing cytochrome c to leak out. The released cytochrome c binds to the apoptotic protease-activating factor-1 (Apaf-1). That complex forms apoptosisome, which activates Caspase-9. Bcl-2 and Bcl-XL can bind to the C terminal part of Apaf-1, thus inhibiting the association of Apaf-1 with Caspase-9. Caspase-9 is one of a family of over a dozen caspases that play a key role in the intrinsic (mitochondrial) pathway of apoptosis [63,64].

Evaluation of EPO renoprotection in renal transplant recipients showed a beneficial effect in preventing chronic renal allograft injury. These protective effects of EPO were associated with preservation of intragraft expression of angiogenic factors, upregulation of the anti-apoptotic factor p-Akt in tubuli, and increased expression of Bcl-2 [65]. EPO plays an important role in the proliferation and differentiation of marrow-derived mesenchymal stem cells (mMSCs) under the AKI microenvironment. Proliferation ability of mMSCs treated with the ischemia/reperfusion (I/R) kidney homogenate supernatant decreased significantly and the apoptosis percentage was significantly higher. Following administration of EPO, mMSCs proliferation increased and the apoptosis percentage decreased. EPO decreased the expression of caspase-3 of mMSCs under the AKI microenvironment in a dose- and time-dependent manner, but increased the Bcl-2 expression [66].

EPO suppressed 6-hydroxydopamine (6-OHDA)-induced apoptosis. 6-OHDA decreased phosphorylation of glycogen synthase kinase 3β (GSK3β) and increased the level of Bax in the mitochondria, which inhibit the protective effect of Bcl-2 [67]. Therefore, administration of EPO upregulated Bcl-2 expression and concurrently diminished expression of Bax, resulting in a net decrease in the ratio of Bax to Bcl-2 protein concentrations [38].

Conclusions

Patients with CKD are a specific group with a high rate of comorbidity, dominated by cardiovascular disease [34,68,69] and other diseases associated with dysfunction of the immune system, which leads to prolonged inflammation and abnormal response to infection [42,70]. The conclusions of the large randomized clinical trials evaluating the effects of EPO-treated patients with CKD and concomitant diseases, have certainly contributed to the development of research on the use of EPO beyond its non-hematopoietic properties. Nephroprotective effects of EPO are achieved by widely related mechanisms of reduction of oxidative stress, apoptosis, and ischemic/reperfusion injury, promotion of vascular repair, or balance of the inflammatory response with subsequent reduction of glomerular and tubular fibrosis.

However, the clinical use of EPO must be balanced against possible adverse effects, especially as relatively high doses of EPO have often been administered to correct anemia of chronic kidney disease [71]. In the light of randomized clinical trials evaluating the safety of EPO, the best possible nephroprotective effect is achievable when it used long-acting erythropoietin in small doses to correct anemia gradually and without exceeding the recommended hemoglobin value of 11-12 g/dl [72,73]. Furthermore, it should be emphasized that the nephroprotection induced by EPO and its long-acting analogues in AKI remains experimental. Clinical trials are needed to assess the efficacy and safety of these drugs in preventing acute kidney injury in humans.

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