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Review

Renoprotective effects of erythropoietin

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Background: Accumulating evidences during the past decade suggest that erythropoietin (EPO) may have many beneficial actions other than on erythropoiesis because many non-hematopoietic cells, including kidney cells, also express EPO receptors.
Objective: To summarize evidences of the renoprotective effects of EPO and review the possible mechanisms of renoprotection provided by EPO.
Results: Experimental studies have demonstrated the renoprotective effects of EPO in acute as well as chronic renal injury models. These renoprotective actions are likely to be mediated by several mechanisms, either directly or indirectly. However, EPO therapy is also associated with adverse effects.
Conclusion: EPO is potentially a novel renoprotective drug. Clinical use of EPO for renoprotection could not be beneficial if adverse side effects of EPO have been overcome.

Keywords: Erythropoietin, kidney disease, renoprotection.

Erythropoietin (EPO) is familiar drugs to practicing nephrologist. From the first purification of human EPO in 1977 [1], EPO rapidly became a principal drug to treat anemia [2]. In addition, accumulating evidence during the past decade suggests that EPO may have many beneficial actions other than erythropoiesis, including action on the kidney, the major source of circulating EPO. This article summarizes experimental evidences of the beneficial effects of EPO on the kidney and suggests possible mechanisms of renoprotection provided by EPO. The potential therapeutic use of EPO as a renoprotective agent is also discussed. For abbreviations, see the last section in the text.

Erythropoietin (EPO): from natural hormone to powerful drug

EPO is a 34 kDa glycoprotein hormone with 165 amino acids [3, 4]. Roughly 30-40 % of the molecular mass is made up of carbohydrate chains that are connected to core polypeptide by 3 N-linked glycosylation on 3 asparagine residues and O-linked glycosylation on 1 serine residue (**Fig. 1**) [5]. These carbohydrate chains especially the terminal sialic acids are important to prevent degradation and delay clearance of EPO from the circulation and are necessary for *in vivo* activity. Deglycosylated EPO and desialated EPO have a very short half-life and very low biological activity *in vivo* while they may remain active *in vitro* [6]. Recombinant human EPO (rHuEPO) used in clinical practice is also highly glycosylated although its carbohydrate chains are not identical to those of the natural EPO. Darbepoetin, a pharmaceutically engineered EPO, has a much longer half-life because it contains more glycosylation sites on the polypeptide backbone and has more carbohydrate chains than the conventional EPO [7, 8].

Circulating EPO in the normal adult is mainly produced by fibroblast-like interstitial cells of the renal cortex [9]. Renal production of EPO increases in response to anemia and hypoxemia. EPO production and secretion by these cells depends on local tissue oxygenation [10]. Although blood flow to the kidney is relatively high, the special arrangement of renal vasculature, that brings renal arterial and venous

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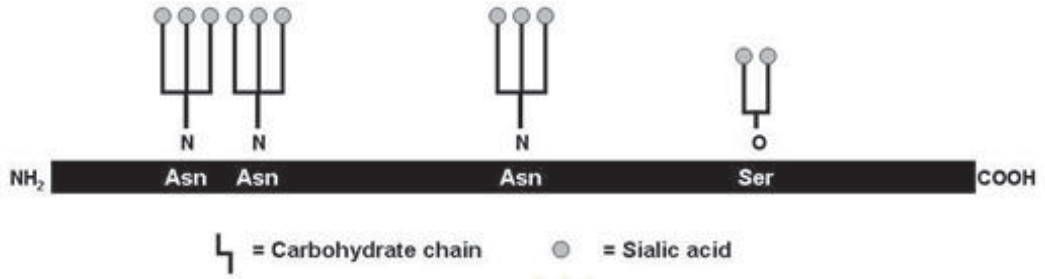

Fig. 1 Structure of erythropoietin. Three N-linked carbohydrate chains are present at asparagines 24, 38, and 83, and one O-linked carbohydrate chain is present at serine 126.

vessels in close parallel contact, allows oxygen to shunt away from the peritubular capillary bed and renders the renal tissue in a low tissue oxygenation state. This low tissue oxygenation makes the renal tissue sensitive to even a small reduction of oxygen delivery caused by anemia or hypoxemia.

Hypoxia-induced expression of EPO is primarily accomplished by a recently discovered transcription factor, the hypoxia inducible factor-1a (HIF-1α) [11]. Under normal oxygenated conditions, HIF-1α is hydroxylated at two conserved proline residues within the central oxygen-dependent degradation domains by the oxygen-dependent prolyl hydroxylase. This prolyl hydroxylation promotes binding of the von Hippel-Lindau tumor suppressor protein, resulting in polyubiquitination and rapid proteasomal degradation of HIF-1α [12, 13]. Moreover, a conserved asparagine residue in the carboxyl-terminal transactivation domain of the HIF-1α is also hydroxylated by factor inhibiting HIF. Asparaginyl hydroxylation of HIF-1α prevents recruitment of the p300/CREB-binding protein transcriptional co-activators leading to reduced transcriptional activation of target genes by the remaining HIF-1α [14]. Under hypoxia, oxygen, an essential substrate for the hydroxylation reactions, is lacking. Therefore, prolyl as well as asparaginyl hydroxylation of HIF-1α are inhibited and the unmodified HIF-1α escapes the degradation cascade, heterodimerizes with HIF-1β, recruits transcriptional co-activators, and up-regulates the transcription of EPO as well as other hypoxia-responsive genes (**Fig. 2**).

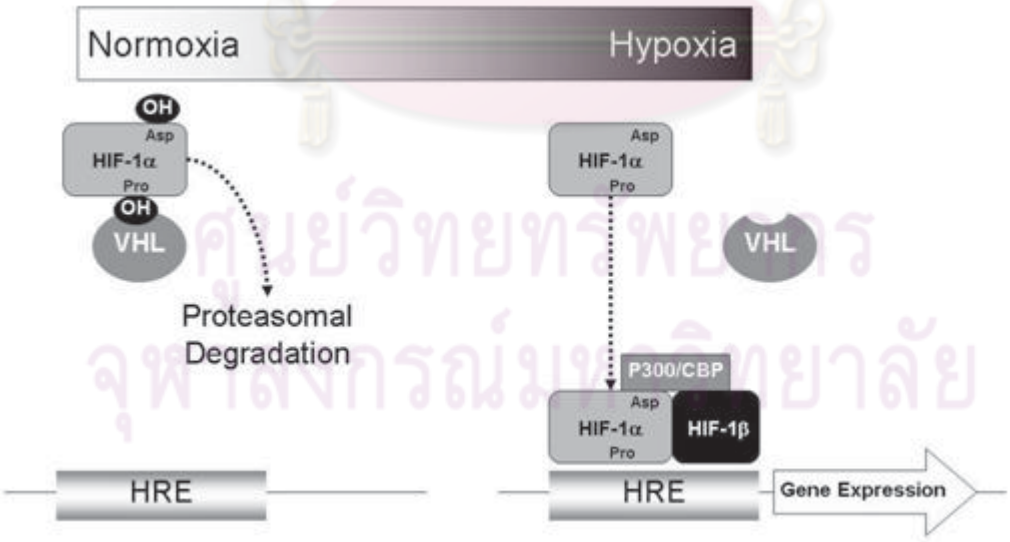

Fig. 2 Mechanisms of hypoxia-induced EPO expression. Under normoxia, HIF-1α is hydroxylated at proline residues by the oxygen-dependent prolyl hydroxylase. This prolyl hydroxylation promotes binding of the von Hippel-Lindau tumor suppressor protein (VHL), resulting in proteasomal degradation of HIF-1α. Additionally, asparagine residue of the HIF-1α is also hydroxylated by factor inhibiting HIF, preventing recruitment of the p300/CREB-binding protein transcriptional co-activators (p300/CBP). Under hypoxia, hydroxylation reactions are inhibited and the unmodified HIF-1α escapes from the degradation cascade, heterodimerizes with HIF-1β, recruits transcriptional co-activators, and up-regulates the transcription of target genes.

The red blood cell production-stimulating effect of EPO was well established long before EPO was purified and characterized. The first purification of human EPO from the urine of an aplastic anemia patient in 1977 led to the cloning of the human EPO gene and permitted mass production of recombinant human EPO [1]. Since its introduction into clinical practice nearly two decades ago, EPO has rapidly become a powerful tool in fighting anemia, especially anemia associated with chronic kidney disease. Currently, anemia remains the sole indication for the therapeutic use of EPO, but, hopefully, therapeutic application of EPO is likely to be expanded in the near future. Studies over the past decade have demonstrated that EPO plays a significant biological role other than in erythropoiesis and have suggested novel non-erythropoiesis applications of EPO.

The hidden power of an old tool

EPO, like other glycoproteins, has little (if any) intrinsic biological activity. It is simply a code, requiring recognition by a receptor and decoding into specific intracellular signaling cascades to exert its biological effects. Hence, the membrane receptor is the key to the physiological actions of circulating EPO. EPO can act only in cells with receptors for EPO and all actions of EPO must be mediated by the receptor.

EPO receptors are present on the cell membrane as a homodimer [15]. The binding of a single EPO molecule to the receptor dimer induces a major conformational change in the receptor, bringing the two Janus kinase 2 (JAK2) molecules, that are tethered to the cytoplasmic portion of the receptor, into close position and thereby activating JAK2 by mutual cross-phosphorylation. Activated JAK2 molecules then induce phosphorylation of tyrosine residues in the cytoplasmic domain of EPO receptor. These phosphorylated tyrosine residues serve as a docking site attracting various intracellular signaling molecules. These secondary signaling molecules are subsequently activated by JAK2-mediated tyrosine phosphorylation and initiate the downstream signal transduction (**Fig. 3**).

Physiologically, activation of EPO receptors on the immature erythroid cells by EPO generates an intracellular signal that promotes the survival of these cells which would otherwise undergo apoptosis. EPO exerts an anti-apoptotic effect via several intracellular signaling pathways (**Fig. 4**). The phosphorylation of signal transducer and activator of transcription 5 (STAT5) leads to its homodimerization, which enables it to enter the nucleus, binds to cis-acting elements and enhances the transcription of various genes, including Bcl-X_L, a gene encoding an antiapoptotic molecule of the Bcl-2 family [16]. The phosphorylation of phosphatidylinositol 3-kinase (PI3-K) activates its kinase activity which in turn phosphorylates protein kinase B (Akt) [17]. Akt will then induce cytoplasmic retention of forkhead box O (FOXO) transcription factors through their phosphorylation, therefore inhibiting proapoptotic molecules, such as Fas ligand or Bim, which are activated by FOXO proteins [18]. Akt will also phosphorylate and inactivate other proapoptotic molecules, including glycogen synthase kinase-3β (GSK3β), caspase 9, or Bad. Moreover, inhibitor of nuclear factor-κB (I-κB) is also phosphorylated by Akt. Phosphorylation of I-κB allows the release of the transcription factor NF-κB, leading to translocation of NF-κB into the nucleus, and activation of many target genes, such as X-linked inhibitor of apoptosis (XIAP) and c-IAP2. EPO also promotes cells proliferation by activation of the Ras/mitogen activated protein kinase (MAPK) pathway [19].

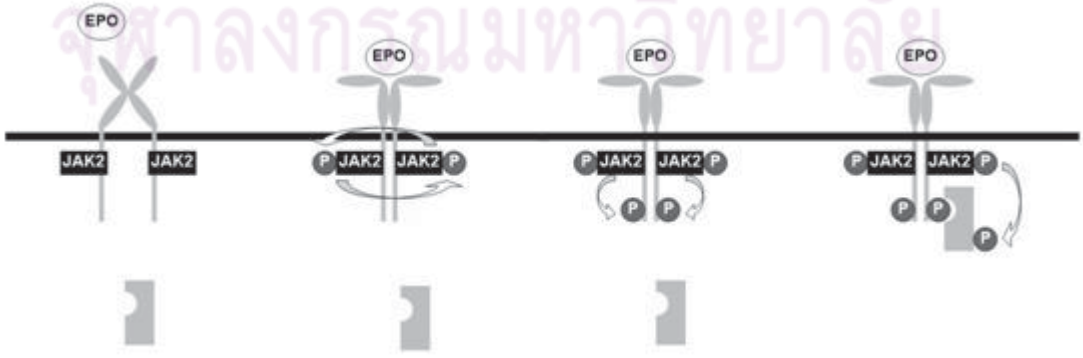

Fig. 3 Activation EPO receptor. EPO receptor exists as a preformed homodimer. Binding of EPO induces conformational changes of the receptor, and activates the associated JAK2 molecules by cross-phosphorylation. Activated JAK2 phosphorylate tyrosine residues in the cytoplasmic domain of the receptor allow binding and phosphorylation of signaling molecules.

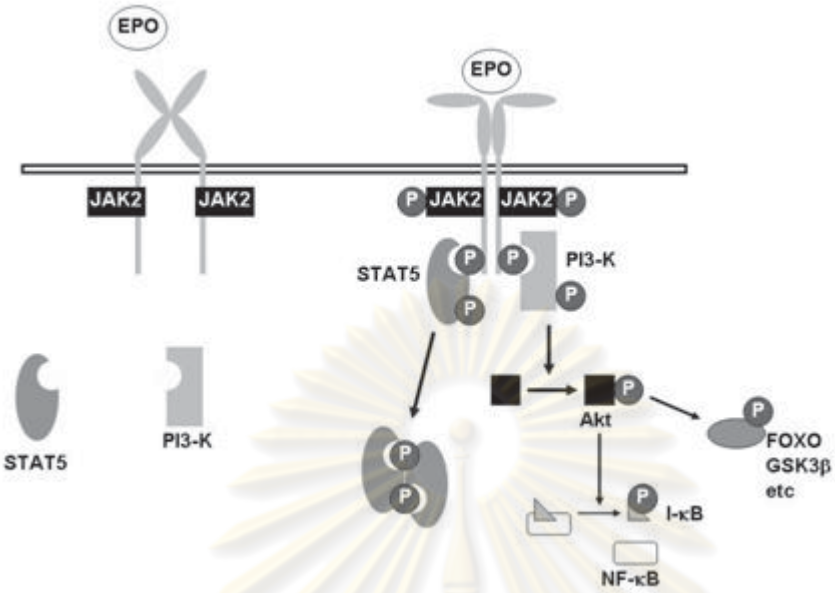

Fig. 4 Anti-apoptotic effect of EPO. Binding of EPO to EPO receptor induces phosphorylation of the STAT5 transcription factors which then homodimerize, translocate into the nucleus, and activate target genes encoding antiapoptotic molecules. It also induces phosphorylation of PI3-K, which in turn phosphorylates Akt. Akt then phosphorylates and inhibits FOXO, GSK-3β, and other proapoptotic molecules. I-κB is also phosphorylated by Akt, which allows the release of the transcription factor NF-κB, and activation of target genes encoding antiapoptotic molecules.

Control of erythropoiesis was once believed to be the only physiological role of EPO. However, later studies showed that several cells outside the hematopoietic system, such as endothelial cells, neural cells, cardiomyocyte and renal cells [20-23], also express receptors for EPO. These findings suggest that EPO may also provide cytoprotection in non-erythropoietic cells and thus stimulate an interest in EPO as a novel therapeutic agent for a number of organs including the kidney, the major producer of EPO circulating in the body.

Renoprotective effect of EPO

Experimental evidence

Several *in vivo* studies have shown that EPO can reduce renal injury in various animal models (**Table 1, 2**). In acute renal injury models, ischemia-reperfusion injury is the most extensively investigated. Although there is some heterogeneity in the protocols for inducing ischemia-reperfusion injury and in the EPO treatment schedules, these studies provide excellent evidence for the renoprotective effect of EPO against acute renal injury. Almost all of these studies have demonstrated that EPO could reduce renal dysfunction and could ameliorate histological changes of acute tubular necrosis. In general, these studies have used relatively high doses of EPO (300 to 5000 U/kg of rHUEPO and 25 mg/kg of darbepoetin). Early EPO treatment, especially before ischemia, seems to provide better results than late EPO administration. However, renoprotection is also observed even when EPO is given as late as 6 hours after reperfusion [24]. Because these studies examine the effects in a relatively short-term, the long-term effects of EPO treatment in this model remain to be determined.

Hypotension and shock are probably the most common causes of ischemia-reperfusion type of renal injury occurring in patients. Systemic shock models may therefore provide more compelling evidence for the renoprotective effect of EPO in a real-life situation. A recent study has revealed that EPO has renoprotective effects in a model of systemic shock induced by hemorrhage [32]. Interestingly, this study could not demonstrate the renoprotective effects of EPO in a model of LPS-induced shock [32]. This discrepancy may reflect the disruption of adaptive responses to the shock in the LPS-induced shock, which EPO could not overcome. Further studies in systemic shock models are encouraging. EPO also provides renoprotection against cisplatin-induced acute renal failure, probably by enhancing tubular regeneration [34].

Table 1. *In vivo* renoprotective effect of EPO: acute renal injury.

Model	EPO treatment	Outcome	Reference
Rat, I/R+Nx (30 or 45 min)	rHuEPO 500 or 3000 U/kg *iv* 0, 24 and 48 after ischemia	↓ Mortality in I/R+Nx (45 min) treated with 3000 U/kg group Serum creatinine same as saline treated group ↑ Hct (48 and 72 hr postischemia)	[25]
Rat, I/R (45 min)	rHuEPO 3000 U/kg *iv* 24 hr before ischemia	↓ Peak serum creatinine ↓ Tubular necrosis ↓ Apoptosis Hct not different	[26]
Rat, I/R (30 min)	rHuEPO 5000 U/kg *ip* 30 min before ischemia	↓ Peak serum creatinine ↓ Apoptosis ↑ Tubular regeneration Hct not different	[27]
Rat, I/R (45 min)	rHuEPO 300 U/kg *iv* 30 min before ischemia, or 5 min before reperfusion, or 30 min after reperfusion (single dose)	↓ Serum creatinine (6 hr after reperfusion) ↑ CrCL and urine flow (6 hr after reperfusion) ↓ Tubular necrosis ↓ Apoptosis Less effective in late EPO group (30 min after reperfusion)	[28]
Rat, I/R (40 min)	rHuEPO 200 U/kg *ip* 0, 6, 24, 48, 72, and 96 hr after ischemia, or 4, 10 and 24 hr after ischemia	↓ Plasma creatinine (2 and 4 day after reperfusion) Prevent down-regulation of AQP and sodium transporters	[29]
Mouse I/R (30 min)	rHuEPO 1000 U/kg *sc* 5 min before reperfusion, or daily x 3 doses before ischemia	↓ Plasma urea and creatinine (24 hr after reperfusion) ↓ Tubular necrosis ↓ MPO activity (reflecting ↓ PMN infiltrate) ↓ Lipid peroxidation Less effective in single dose 5 min prereperfusion group	[30]
Rat, I/R (45 min)	rHuEPO 500 U/kg *ip* 20 min before ischemia	↓ Serum urea and creatinine (48 hr after reperfusion) ↓ tubular necrosis ↓ apoptosis	[31]
Rat, I/R (45 min)	rHuEPO 5000 U/kg, or Darbepoetin 25 μg/kg *ip* at time of ischemia, or 6 hr after reperfusion	↓ Peak plasma urea and creatinine Tubular necrosis not different ↓ Apoptosis ↑ Tubular regeneration ↑ Hct	[24]
Rat, Hemorrhagic shock	rHuEPO 300 U/kg *iv* 5 min before resuscitation	↓ Serum urea and creatinine (4 hr after resuscitation) ↓ Caspase 3, 8 and 9	[32]
Rat, Endotoxic shock	rHuEPO 300 U/kg *iv* 30 min before LPS injection	Serum urea and creatinine not different (6 hr after LPS)	[32]

Table 1. *In vivo* renoprotective effect of EPO: acute renal injury (continued).

Model	EPO treatment	Outcome	Reference
Rat, Cisplatin (7 mg/kg)	rHuEPO 100 U/kg *ip* daily x 9 dose after cisplatin	↑ CrCL and InCL (9 day after cisplatin) ↑ Tubular regeneration ↑ Hct	[33]
Rat, Cisplatin (6 mg/kg)	rHuEPO 100 U/kg *ip* daily x 9 dose after cisplatin	↑ GFR and RBF (9 day after cisplatin) Tubular damages not different ↑ Tubular regeneration ↑ Hct	[34]
Rat, CIN (Iothalamate)	rHuEPO 3000 U/kg *iv* 24 hr then 600 U/kg *iv* 2 hr before CIN protocol	Prevent ↓ CrCL (1 day after CIN)	[35]

I/R+Nx = left nephrectomy and ischemia-reperfusion injury to right kidney (ischemic time in parenthesis); I/R = bilateral ischemia-reperfusion injury (ischemic time in parenthesis); CIN = contrast medium-induced nephropathy protocol (indomethacin 10 mg/kg intravenous followed by nitro-L-arginine methylester 10 mg/kg intravenous at 15 min and 30 min, then meglumine iothalamate 6 ml/kg intraarterial); iv = intravenously; ip = intraperitoneally, sc = subcutaneously; Hct = hematocrit; CrCL = creatinine clearance; InCL = inulin clearance; MPO = myeloperoxidase; PMN = polymorphonuclear; LPS = lipopolysaccharide; GFR = glomerular filtration rate; RBF = renal blood flow.

A recent study has demonstrated that EPO could protect the kidney from chronic renal injury as well. Long-term therapy of low-dose darbepoetin could reduce mortality, renal dysfunction, and renal scarring in rats with the remnant kidney model (5/6 nephrectomy) [36]. This renoprotection is not associated with erythropoiesis effect since hemotocrit in the darbepoetin treated group is similar to the saline-treated group. Another report using standard dose darbepoetin similarly provides renoprotection in remnant kidney model, but this occurs in association with increasing hematocrit [37]. Studies in chronic cyclosporine nephropathy and doxorubicin-induced cardiorenal injury have also revealed renoprotection by EPO [38, 39]. A recent preliminary report has also found that EPO could effectively reduce tubulointerstitial injury in the Dahl salt-sensitive rats fed with low salt diet [41]. Unfortunately, a previous study using a radiation-induced nephropathy model has failed to demonstrate renoprotection of EPO given during radiation [40]. Moreover, the peri-radiation EPO treatment used in this study may, in fact, worsen the renal injury. Since cancer patients requiring radiation therapy usually receive EPO to treat anemia, this potentially adverse effect of EPO during the radiation period needs to be further clarified. Other treatment schedules to prevent radiation nephropathy including long-term EPO treatment after radiation should also be examined.

Mechanisms of renoprotection

Like any other organ system in the body, the kidney is not simply the mathematical sum of all its parts. To maintain appropriate function in our tough and ever-changing world, every cell in the kidney must be well-coordinated and work together in a right way at the right time, either by electrical signal through intricate nerves or by chemical signaling through cytokines and hormones. The kidney also needs integrated supports from other organ systems. For instance, the kidney depends on the cardiovascular system to provide adequate tissue perfusion. It also relies on the respiratory system and red blood cells to maintain adequate oxygen delivery. Therefore, the renoprotective effect of EPO can be divided into direct cytoprotective effect on renal cells and indirect beneficial effects from improving these coordinate works (**Table 3**).

EPO has two notable direct cellular effects: anti-apoptosis and mitogenesis. Several studies have clearly demonstrated that EPO significantly reduces renal apoptotic cell death by stimulation of anti-apoptotic molecules and inhibition of proapoptotic molecules [24, 26-28, 31, 32, 36, 38, 46]. Although apoptosis is almost always equivalent to a death sentence for the cells, it probably has a beneficial role for the functioning organs and ultimately the living organisms. Cells usually have a good reason when

Table 2. *In vivo* renoprotective effect of EPO: chronic renal injury.

Model	EPO treatment	Outcome	Reference
Rat, 5/6 Nephrectomy	Darbepoetin 0.1 μg/kg *sc* Once weekly after renal mass reduction	↓ Mortality ↓ Serum creatinine and urinary protein excretion (6 wk) ↓ Vascular, glomerular and tubulointerstitial damage ↓ Loss of peritubular capillary ↓ ApoptosisHct not different ↓ Systolic blood pressure	[36]
Rat, 5/6 Nephrectomy	Darbepoetin 0.4 μg/kg *sc* Once weekly after renal mass reduction	↓ Serum creatinine (12 wk) ↓ Renal scarring ↓ Loss of peritubular capillary ↑ VEGF expression ↑ Hct	[37]
Rat, Cyclosporine (15 mg/kg/d)	rHuEPO 100 U/kg *sc* Thrice weekly	Serum creatinine and CrCL not different (4 week) ↓ Tubulointerstitial inflammation and fibrosis ↓ Apoptosis Tubular regeneration not different ↓ Osteopontin and transforming growth factor-β ↑ Hct Systolic blood pressure not different	[38]
Rat, Doxorubicin (3 mg/kg follow by 2 mg/kg 2 week later)	Darbepoetin 3 or 30 μg/kg *sc* Once weekly 2 week after last dose of doxorubicin	↓ Serum urea and creatinine (11 wk) ↑ CrCL ↓ Tubulointerstitial fibrosis ↓ Iron deposition ↑ Urinary total radical-trapping antioxidant capacity ↑ Hct Systolic blood pressure not different	[39]
Mouse, Radiation (6, 8 or 10 Gy)	rHuEPO 500 or 2000 U/kg *sc* 18 and 2 hr before, and 23 hr after radiation	↑ Loss of renal function	[40]

Hct = hematocrit; VEGF = vascular endothelial growth factor; CrCL = creatinine clearance.

Table 3. Possible renoprotective effect of EPO.

EPO actions	Possible protective effects
Direct	
Anti-apoptosis	Increase cells survival, reduce tissue injury
Mitogenesis	Enhance repairing processes
Indirect	
Erythropoiesis	Improve oxygen delivery, reduce hypoxic injury (if anemia)
EPC mobilization [42]	Stimulate angiogenesis, enhance endothelial reapir
NO release [43, 44]	Vasodilatation, improve tissue perfusion and oxygenation
VEGF expression [45]	Stimulate angiogenesis, enhance endothelial repair

EPC = endothelial progenitor cell; NO = nitric oxide; VEGF = vascular endothelial growth factor.

they undergo apoptosis, such as when they are severely damaged. Thus, anti-apoptosis may benefit the organism if the cells are saved from the injuries and do not need to undergo apoptosis, but anti-apoptosis may not really benefit the organism if the appropriate apoptotic signals of severely injured cells are simply hijacked and the handicapped malfunctioning cells live indefinitely. Hopefully, EPO exerts its anti-apoptotic effect by the former mechanism. EPO has been reported to increase cellular anti-oxidative defense by stimulating glutathione peroxidase activity [47]. A recent preliminary report has also suggested that EPO may reduce oxidative stress by up-regulation of heme oxygenase, an important cellular anti-oxidant enzyme [41]. Furthermore, EPO may also help to maintain mitochondrial membrane potential and thus may prevent cytochrome C release from mitochondria during anoxic injury [48]. Anti-apoptotic effect of EPO, therefore, should be regarded as a *marker* of cellular protection, instead of a *principal mechanism* of cytoprotection. The mitogenic effect of EPO may provide direct renoprotection by enhancing the repairing processes after renal injury. Several studies have confirmed the EPO-induced mitogenic effect in endothelial cells and renal cells [20, 23, 24, 27, 34].

There are several indirect renoprotective effects of EPO. Anemia is frequently associated with kidney disease which may exacerbate more renal hypoxia and progression of chronic kidney disease [49, 50]. Thus, EPO-induced erythropoiesis likely provides renoprotection by improving oxygen delivery, reducing hypoxic injury. Clinical studies have demonstrated that EPO treatment to correct anemia could improve renal survival in CKD patients [51, 52]. Patients with polycystic kidney disease usually have progressive renal failure despite increased EPO production and enhanced erythropoiesis [53-55]. Nevertheless, it is not clear whether these findings only reflect the nature of the polycystic disease that is still progressive even when the kidney have been protected by EPO, or they do demonstrate the lack of renoprotective effect of EPO. EPO action on endothelial progenitor cells (EPC) in bone marrow may also provide indirect renoprotection by stimulating EPC mobilization which stimulates angiogenesis and enhances endothelial repair [42]. Modulation of other cytokines, such as nitric oxide and vascular endothelial growth factor (VEGF), is potentially another indirect renoprotective action of EPO. A recent study using darbepoetin therapy in remnant kidney rat models has shown an increased renal VEGF expression associated with better preservation of renal function and structure including microvascular density [37].

Dark side of the powerful tool

In the evolutionary perspective, organisms are shaped by natural selection of the fittest, and every organism is usually equipped with almost perfect biological processes. If EPO protects cells from injury, why do we have to give it? Why is EPO not expressed constitutively at a higher level ? The answer might be that EPO also has adverse effects. Too much EPO may cause erythrocytosis and may increase blood viscosity as well as potential for thrombosis. EPO can also promote endothelin mediated-renal vasoconstriction and hypertension [56]. Moreover, some cancer cells especially renal carcinoma cells, express EPO receptors and, thus, EPO may have anti-apoptotic and mitogenic effects on these cells and may adversely cause tumor progression [57]. Therefore, clinical use of EPO must be balanced against these possible adverse effects, especially when used at a relatively high dose as in some animal studies [24, 26, 27].

The new hope

Novel derivatives of EPO that are still cytoprotective but do not stimulate significantly erythropoiesis have been developed. Desialylated EPO, which possesses a very short plasma half-life, has fully neuroprotective effects despite reducing its erythropoiesis [58].

Another novel EPO derivative, carbamylated EPO, is a heteromeric receptor-specific ligand. It does not bind to the classical EPO receptor homodimer and does not show any hematopoietic activity in human cell signaling assays or upon chronic dosing in different animal species [59]. Nevertheless, carbamylated EPO is cytoprotective *in vitro* and confers *in vivo* neuroprotection and cardioprotection in potency and efficacy comparable to EPO [59, 60]. A subsequent study has shown that tissue protective effects of EPO are mediated through its binding to heterodimers containing the EPO receptor and the common beta receptor. Both EPO and carbamylated EPO bind to these heteroreceptors and exert tissue protective effects [61]. Further work is required to determine how these heteroreceptors trigger intracellular signaling.

That carbamylated EPO does not bind to the classical EPO receptor also causes markedly different procoagulant and vasoactive activities between carbamylated EPO and rHuEPO. Carbamylated EPO increases renal blood flow, promotes sodium excretion, reduces injury-induced elevation in procoagulant activity, while not affecting platelet production. In contrast, rHuEPO increases systemic blood pressure, reduces regional renal blood flow, and increases platelet counts and procoagulant activities [62].

EPO use for renoprotection in chronic kidney disease (CKD) deserves considerations. Since CKD is often associated with anemia, the erythropoiesis effect of EPO becomes less unfavorable in CKD. Primary concern about the use of EPO for renoprotection in CKD is probably EPO-associated hypertension which may cause renal injury and negate the renoprotective effect of EPO. One possible solution is the combination therapy of rHuEPO and antihypertensive drugs. Recently, antihypertensive drugs, especially angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB), have been shown to be effective in prevention of hypertension and renal histologic damage in uemic rats receiving rHuEPO to correct anemia [63]. However, addition of ACEI and/or ARB to rHuEPO therapy is more complicated than previously thought. Recent evidences suggest that angiotensin II, a volume regulatory signal, may directly stimulate erythropoiesis [64-66]. Therefore, ACEI and ARB treatment may increase rHuEPO requirement to achieve a particular level of hematocrit [67]. On one hand, this effect may be undesirable because of the additional rHuEPO cost, but on the other hand, it would be desirable since one can receive more rHuEPO for renoprotection with less erythrocytosis.

The renoprotective effects of these novel EPO derivatives and combination therapy with EPO and antihypertensive drugs need to be investigated. Their potential usefulness represents new hope for new renoprotective therapies with less adverse effects.

Conclusion

Although experimental evidences for the renoprotection of EPO are impressive, clinical studies to confirm these experimental data are still lacking, probably due to the concern about the adverse effects of high dose EPO. Novel EPO derivatives with reduced adverse effects may help to accelerate the translation of these robust experimental data into clinical practice.

List of abbreviations

ACEI = angiotensin converting enzyme inhibitor,
ARB = angiotensin receptor blocker,
CIN = contrast medium-induced nephropathy,
CrCL = creatinine clearance,
EPC = endothelial progenitor cell,
EPO = Erythropoietin,
FOXO = forkhead box O,
GFR = glomerular filtration rate,
GSK3β = glycogen synthase kinase-3β,
Hct = hematocrit,
HIF-1α = hypoxia inducible factor-1α,
I-κB = inhibitor of nuclear factor-κB,
I/R = ischemia-reperfusion injury,
I/R+Nx = left nephrectomy and ischemia-reperfusion injury to right kidney,
InCL = inulin clearance,
JAK2 = Janus kinase 2,
LPS = lipopolysaccharide,
MAPK = mitogen activated protein kinase,
MPO = myeloperoxidase,
NF-κB = nuclear factor-κB,
NO = nitric oxide,
PI3-K = phosphatidylinositol 3-kinase,
PMN = polymorphonuclear
RBF = renal blood flow
rHuEPO = recombinant human EPO,
STAT5 = signal transducer and activator of transcription 5,
VEGF = vascular endothelial growth factor,
VHL = von Hippel-Lindau tumor suppressor protein,
XIAP = X-linked inhibitor of apoptosis.

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