

Reno-protective Effect of Erythropoietin (EPO) : Possibly Via an Amelioration of Renal Hypoxia with Stimulation of Angiogenesis in the Kidney

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Background : Renal hypoxia with loss of microvasculature plays a key role in progression of renal disease via the production of extracellular matrix, inflammatory cell infiltration and afferent arteriopathy. Recently, administration of EPO in chronic renal failure patients has been reported to result in better renal survival with a correction of anemia. The mechanisms of the beneficial effect of EPO on patients' survival may be related to an increased oxygen delivery to tissues and reduction of hypoxia with anemia correction or any other direct effect of EPO.

Methods and Results : In order to examine the reno-protective effect of EPO with potential mechanisms, we administered subcutaneous rHuEpo (100 U/kg/week) into 5/6 remnant kidney rats (RK) after renal mass reduction, and sacrificed the rats at 1, 2 and 12 weeks of EPO administration. RK+EPO rats showed a higher hematocrit from 4 weeks after EPO compared to RK+vehicle rats. EPO treatment in RK rats was associated with better preservation of renal function at 12 weeks after renal mass reduction (serum creatinine 1.5 ± 617 ; 0.5 vs. 2.6 ± 617 ; 0.6 mg/dL, RK vs. RK+EPO, $p < 0.05$) with less renal scarring. Microvascular density and endothelial cell proliferation in glomerulus and tubulointerstitium were significantly higher in RK+EPO rats compared to RK+vehicle rats. Renal cortical VEGF expression was also higher in RK+EPO rats. In-vitro experiment with renal tubular cells (mTAL cells) showed a proliferative response with EPO (0.1-100 U/mL) with an up-regulation of VEGF expression. EPO also prevented hypoxia-induced apoptosis of mTAL cells.

Conclusion : In conclusion, EPO treatment in animal model of chronic renal failure was associated with better preservation of renal function and structure. Possible mechanisms for this reno-protective effect of EPO may be related to amelioration of renal hypoxia not only by correcting anemia but also by enhancing renal microvascular cell survival and/or angiogenesis. Direct pro-survival effect of EPO on renal tubular cell with up-regulation of VEGF expression can be also an important mechanism of this unexpected renal action of EPO.