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The importance of erythropoietin in diabetic retinopathy

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In the present study, we investigated the beneficial effects of epoetin delta, as a new EPO analogue, on oxidative stress in target tissues susceptible to diabetic complications and further focused on vascular and neuronal changes in the diabetic retina.

The first part of the study was aimed to investigate the dose effect of epoetin delta on blood parameters, such as hematocrit and the antibody formation against epoetin delta to define a feasibility of a long-term treatment with epoetin delta. One weekly dose of epoetin delta with two different application frequencies (1x384 I.U./kg and 3x128 I.U./kg, i.p.) was administered over a period of 3 months to streptozotocin-induced diabetic rats. Our data showed that both epoetin delta treatment regimes did not affect hematocrit and blood glucose level, did not induce anti-EPO antibody formation, and did not alter body weight. Epoetin delta treatment had anti-oxidative properties in the retina, kidney and heart, which are typically damaged by hyperglycemia. Moreover, epoetin delta treatment at higher frequency (D+HF, D+3x128 I.U.) prevented early pericyte loss in the diabetic retina.

Long-term EPO treatment with erythropoietic doses is clinically associated with increased rates of thrombosis and the development of hypertension. In the second part, the assessment of epoetin delta treatment with suberythropoietic dose did not affect blood pressure. We also found that epoetin delta treatment did not reduce increased leucostasis in the diabetic retina, which is thought to mediate endothelial damage.

In the third part of the study, we studied the effect of long-term epoetin delta treatment in experimental diabetes. Diabetic rats were treated with two suberythropoietic doses of epoetin delta (3 x 256 U/kg and 3 x 128 U/kg per week, i.p.) for 6 months.

We used retinal digest preparations and quantitative retinal morphometry to assess the morphological consequences of long-term epoetin delta treatment. There was no measurable effect on endothelial cells, but we observed a 9% pericyte loss after 3 months and a 22% loss of pericytes after 6 months of diabetes. Epoetin delta treatment completely normalized pericyte loss after 3 months, and partially (50%) restored pericyte loss after 6 months. Of note, long-term epoetin delta treatment was able to abolish the formation of acellular capillaries after 6 months of diabetes.

Another important aspect of EPO is neuroprotection. To this end, we investigated neuronal apoptosis and signs of neurodegeneration in diabetic rats with and without epoetin delta treatment. Our data indicate an almost complete protection of the retina from hyperglycemia- induced neurodegeneration by long-term epoetin delta treatment.

The upregulated VEGFA level in the diabetic retina was reduced by epoetin delta treatment after 3 and 6 months, and epoetin delta reduced the HSP27 expression, which is expressed in astrocytes and Mueller cells under stress. The increased methylglyoxal level by hyperglycemia was normalized by 3 months of epoetin delta treatment.

In summary, the findings of this study provide evidence that erythropoietin exerts strong vascular- and neuroprotective effect in the diabetic retina. Application of exogenous EPO reduced oxidative stress in diabetic tissues, and furthermore protected from vascular damage and neurodegeneration in experimental diabetic retinopathy. Moreover, EPO treatment reduced the accumulation of methylgloxal-type AGEs as well as VEGF expression in the diabetic retina, which the reduction of VEGF expression by epoetin delta indicates a decreased need for vascular- and neuroprotective survival factor.

Taken together, this is the first experimental study showing that epoetin delta, besides its beneficial clinical effect in CKD patients, is also effective to protect vascualr and neuronal damage in the experimental diabetic retina. These preliminary data suggest that suberythropoietic doses of EPO over extended periods are beneficial for the diabetic retina, and suggest that the prevention of vasoregression is possible with much lower doses than previously assumed.