EFFECT OF ERYTHROPOIETIN RECEPTOR SIGNALING ON RETINAL GANGLION CELL NUMBER AND VISUAL ACUITY AFTER OXYGEN-INDUCED DAMAGE

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Purpose: Premature infants are at risk of developing vision-threatening retinopathy of prematurity (ROP), which can result in lifelong vision impairment and is one of the leading causes of childhood blindness. Clinical studies have shown that one-third of infants with severe ROP develop childhood glaucoma, a disease associated with degeneration of retinal ganglion cells (RGCs). RGCs are critical for detecting features of vision and transmitting visual information to the brain. Recent studies have demonstrated that Erythropoietin (EPO) signaling through its receptor (EPOR) may be neuroprotective. The purpose of this study was to test the hypothesis that EPOR signaling protects RGCs and preserves functional vision against oxygen stresses experienced by infants born prematurely that develop ROP.

Methods: A mouse oxygen-induced retinopathy (OIR) model was used to represent the oxygen stresses experienced by the retina in ROP in which juvenile mice were placed in a high oxygen environment (75% O₂) for 5 days (from postnatal day (P) 7 to P12) then returned to room air. To test the effects of EPOR signaling, transgenic mice with reduced EPOR signaling (EPOR<sub>low</sub>) were compared to wildtype littermate controls (EPOR<sub>wt</sub>). At 8 weeks of age, visual acuity thresholds were determined using the OptoMotry System (CerebralMechanics, Inc.). Visual acuity threshold was defined as the highest grating frequency (cycles/degree, c/d) responded to by the mouse. The optic nerve thickness, made up of RGC axon projections to the brain, was measured in micrometers (µm) after whole eye enucleation. Whole retinas were then stained with the RGC marker RBPMS and imaged with a confocal microscope. RGC counts were manually performed using ImageJ software. Data were statistically analyzed using a two-tailed t-test with a significance level of 0.05.

Results: The study found that visual acuity significantly decreased in OIR model compared to room air (RA) controls (p<0.001), but there were no significant differences when comparing EPOR<sub>low</sub> and EPOR<sub>wt</sub> mice in OIR or RA (OIR p=0.339; RA p=0.107). Likewise, optic nerve was significantly thinned in OIR compared to RA mice (p<0.05), but there was no difference in thickness between EPOR<sub>low</sub> and EPOR<sub>wt</sub> in OIR or RA conditions (OIR p=0.395; RA p=0.472). Lastly, there was a significant decrease in central RGC counts in EPOR<sub>low</sub> compared to EPOR<sub>wt</sub> mice in OIR (p<0.05), and a significant increase in central RGC count in EPOR<sub>low</sub> compared to EPOR<sub>wt</sub> mice in RA (p<0.05).

Conclusion: The current model suggests that EPOR signaling may have an effect on RGC number but does not affect optic nerve thickness, or visual acuity in oxygen induced damage. The differences observed between OIR and RA give evidence that oxygen stresses contribute to reduced RGC health and visual function.