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Early mechanisms of retinal degeneration in a mouse mimic of oculodentodigital dysplasia (ODDD)-related glaucoma

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Oculodentodigital dysplasia (ODDD) is a human disease with glaucoma due to mutations in the connexin43 (Cx43) gene GJA1. Gja1^{Jrt}/+ mice have a G60S substitution with a dominant negative effect on wild-type connexin43 gap junction formation. Previously, we compared the ocular phenotypes of 37Gja1^{Jrt}/+ mice to age-matched, wild-type mice (1 to 48 weeks of age) using ocular coherence tomography and intraocular pressure assessments with post mortem ocular histological examination. Ocular disease initiates with deformation of the ciliary body and progresses to retinal degeneration. The retinal pigmented epithelium, a major component of the blood:retinal barrier (BRB), is well coupled with the Cx43 protein. It is unknown what BRB effects the G60S mutation has in Gja1^{Jrt}/+ mice. Here, we confirm anterior origins of ODDD retinal degeneration and rule out a hypothesis of compromised (BRB). BRB integrity was assessed in fiveGja1^{Jrt}/+ mice with advanced disease compared to age-matched, wild-type mice. Intravenous injection of Evans Blue dye (EB; 45 mg/kg) with a 30 minute circulation period followed by post mortem phosphate-buffered salineperfusion was used to detect EB presence in retina, brain and liver. Formamide was used to recover EBfor spectrophotometric assessment of tissue EB concentration (peak and background absorbance at 620 and 740 nm, respectively). Background-subtracted absorbance values in retina were normalized to 1 mg of tissue and, using standard curves, EB concentration values were calculated and normalized for liver EB concentration. Genotypes and tissues were compared to detect significant differences (two-factor ANOVA, $p<0.05$). Elevatedliver EB concentrations confirmed assay performance. Unchanged retinal and brain EB concentrations are consistent with no loss of BRB and blood:brain barrier integrity in Gja1^{Jrt}/+ mice. Overall, ocular disease onset and progression in Gja1Jrt/+ mice are consistent with disease mechanisms originating in the anterior segmentation culminating in retinal degeneration with retention of BRB integrity.

Biography

Mohammad Ali Faraz is currently studying Medical Sciences at Western University, Canada. He was awarded two Natural Sciences and Engineering Council of Canada Undergraduate Summer Research Awards. Starting in 2012, Ali contributed toresearch projects under the supervision of Dr. Kathleen Hill (Biology, Western Ontario) with a focus on understanding early mechanisms of retinal degeneration in murine models. He was awarded the 2013 Best Oral Presentation at the Annual London Region Ophthalmology Research Day Conference. Currently, he is comparing human and mouse models of mitochondrial dysfunction leading to retinal degeneration.

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