Vision deficits precede structural losses in a mouse model of mitochondrial dysfunction and progressive retinal degeneration

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Current animal models of retinal disease often involve the rapid development of a retinal disease phenotype; however, this is at odds with age-related diseases that take many years to manifest clinical symptoms. The present study was performed to examine an Apoptosis-inducing factor (Aif)-deficient model, the harlequin carrier mouse (X(hq)X), and determine how mitochondrial dysfunction and subsequent accelerated aging affect the function and structure of the mouse retina. Vision and eye structure for cohorts of 6 X(hq)X and 6 wild type mice at 3, 11, and 15 months of age were studied using in vivo electroretinography (ERG), and optical coherence tomography (OCT).

Retinal superoxide levels were determined in situ using dihydroethidium (DHE) histochemistry. Retinal cell counts were quantified post mortem using hematoxylin and eosin (H&E) staining. ERG analysis of X(hq)X retinal function indicated a reduction in b-wave amplitude significant at 3 months of age (p < 0.05), declining further with age. However, retinal neuron counts demonstrated the absence of physical degeneration at 3 and 11 months of age despite significant reduction in ERG b-wave amplitude.

Superoxide anion levels were elevated in the ganglion cell, inner nuclear and outer nuclear layers of the retina (p < 0.01, p < 0.01, and p < 0.001, respectively) of 11-month-old X(hq)X mice in comparison to wild type, preceding the structural losses observed at 15 mos. Early onset of retinal function deficits occurred independently of neuron loss. Changes in neurotransmitter localization in the stressed retina may account for the early and significant reduction in retinal function.

This remodeling of retinal neurochemistry in response to stress may be a relevant mechanism in the progression of normal retinal aging and early stages of some retinal degenerative diseases.

PMID: 21983042