AB018. Ocular hypertension promotes early mitochondrial fragmentation in retinal endothelial cells in a mouse model of glaucoma

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Background: Retinal endothelial cells are very active and contribute to the integrity of the neurovascular unit. Vascular dysfunction has been proposed to contribute to the pathogenesis of glaucoma. Here, we evaluated the hypothesis that ocular hypertension triggers mitochondrial alterations in endothelial cells impairing the integrity of the blood retinal barrier (BRB).
Methods: Ocular hypertension was induced by injection of magnetic microbeads into the anterior chamber of EndoMito-EGFP mice, a strain expressing green fluorescent protein selectively in the mitochondria of endothelial cells. Capillary density, mitochondrial volume, and the number of mitochondrial components were quantified in 3D-reconstructed images from whole-mounted retinas using Imaris software. Dynamin-related protein (DRP-1), mitofusin-2 (MFN-2) and optic atrophy-1 (OPA-1) expression were assessed by western blot analysis of enriched endothelial cells. Mitochondrial structure was evaluated by transmission electron microscopy (TEM) and oxygen consumption rate was monitored by Seahorse analysis. The integrity of the BRB was evaluated by quantifying Evans blue leakage.
Results: Our data demonstrate that two and three weeks after ocular hypertension induction, the total mitochondria volume in endothelial cells decreased from 0.140±0.002 μm^3 from non-injured retinas to 0.108±0.005 and 0.093±0.007 μm^3, respectively in glaucomatous eyes (mean ± S.E.M, ANOVA, $P<0.001$; N=6/group). Frequency distribution showed a substantial increase of smaller mitochondria complexes (<0.5 μm^3) in endothelial cells from glaucomatous retinas. Significant upregulation of DRP-1 was found in vessels isolated from glaucomatous retinas compared to the intact retinas, while MFN-2 and OPA-1 expression was not affected. Structural alteration in endothelial cell mitochondria was confirmed by TEM, which were accompanied by a 1.93-fold reduction in the oxygen consumption rate as well as 2.6-fold increase in vasculature leakage in glaucomatous retinas (n=3–6/group). In addition, this model did not trigger changes in the density of the vascular network, suggesting that mitochondrial fragmentation was not due to endothelial cell loss.
Conclusions: This study shows that ocular hypertension leads to early alterations in the dynamic of endothelial cell mitochondria, contributing to vascular dysfunction in glaucoma.

Keywords: Glaucoma; endothelial cells; mitochondria; vascular leakage

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