

Impairment of Membrane Repolarization Accompanies Axon Transport Deficits in Glaucoma

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Glaucoma is a leading cause of blindness worldwide, resulting from degeneration of retinal ganglion cells (RGCs) , which form the optic nerve. In glaucoma, axon transport deficits appear to precede structural degeneration of RGC axons. The period of time between the onset of axon transport deficits and the structural degeneration of RGC axons may represent a therapeutic window for the prevention of irreversible vision loss. However, it is unclear how deficits in axon transport relate to the electrophysiological capacity of RGCs to produce and maintain firing frequencies that encode visual stimuli.

Here, we examined the electrophysiological signature of individual RGCs in glaucomatous retina with respect to axon transport facility. Utilizing the Microbead Occlusion Model of murine ocular hypertension, we performed electrophysiological recordings of RGCs with and without deficits in anterograde axon transport. We found that RGCs with deficits in axon transport have a reduced ability to maintain spiking frequency that arises from elongation of the repolarization phase of the action potential. This repolarization phenotype arises from reduced cation flux and K⁺ dyshomeostasis that accompanies pressure-induced decreases in Na/K-ATPase expression and activity. In vitro studies with purified RGCs indicate that elevated pressure induces early internalization of Na/K-ATPase that, when reversed, stabilizes cation flux and prevents K⁺ dyshomeostasis.

Furthermore, pharmacological inhibition of the Na/K-ATPase is sufficient to replicate pressure-induced cation influx and repolarization phase phenotypes in healthy RGCs. These studies suggest that deficits in axon transport also likely reflect impaired electrophysiological function of RGCs. Our findings further identify a failure to maintain electrochemical gradients and cation dyshomeostasis as an early phenotype of glaucomatous pathology in RGCs that may have significant bearing on efforts to restore RGC health in diseased retina.

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Front Neurosci. 2019 Nov 1;13:1139. doi: 10.3389/fnins.2019.01139. eCollection 2019.

<http://www.ncbi.nlm.nih.gov/pubmed/31736686>