

# Decreased Energy Capacity and Increased Autophagic Activity in Optic Nerve Axons With Defective Anterograde Transport

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**PURPOSE:** Autophagy is a critical process, compromised in neurodegenerative disease, by which terminally differentiated cells like neurons manage cytoskeletal and organelle turnover. How autophagy relates to associated neurodegenerative pathologies remain unclear. We examined autophagy in optic neuropathy by investigating cytoskeletal degradation, mitochondria, and autophagic vesicles in the DBA/2J mouse model of glaucoma exhibiting differing levels of axon transport functionality.

**METHODS:** DBA/2J and DBA/2Jwt-gpnmb control mice 11 to 14 months of age were injected with cholera toxin-B (CTB) to assay anterograde axonal transport. Axonal mitochondria and autophagic vesicles were analyzed with respect to transport integrity in proximal and distal optic nerve using serial block face scanning electron microscopy (3D EM) .

**RESULTS:** Several indices varied significantly between the DBA/2J and DBA/2Jwt-gpnmb mice, including mitochondrial volume, average number of autophagic vesicles per axon, and mitochondrial cristae. However, there were no differences in mitochondrial cristae for axons with functional versus dysfunctional CTB transport, suggesting that mitochondrial dysfunction precedes overt transport blockade. Anterograde transport failure was accompanied by a dissociation of the relationship between mitochondrial and axon volumes. Autophagic vesicle profiles were significantly increased in optic nerve with transport deficit, consistent with greater autophagic activity. Mitochondria within autophagosomes, indicative of mitophagy, were observed in both proximal and distal axons.

**CONCLUSIONS:** Loss of anterograde transport in DBA/2J optic nerve is concomitant with diminished mitochondrial volume, increased cytoskeletal breakdown and autophagic activity, and accumulation of autophagic profiles, including signs of mitophagy, in proximal optic nerve. Axons with transport deficit are metabolically underserved, though not necessarily from mitophagy.

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