AB015. Metabolic stress in glaucoma engages early activation of the energy biosensor adenosine monophosphate-activated protein kinase leading to neuronal dysfunction

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Background: Metabolic stress has been proposed to contribute to neuronal damage in glaucoma, but the mechanism driving this response is not understood. The adenosine monophosphate-activated protein kinase (AMPK) is a master regulator of energy homeostasis that becomes active at the onset of energy stress. AMPK is a potent inhibitor of the mammalian target of rapamycin complex 1 (mTORC1), which we showed is essential for the maintenance of retinal ganglion cell (RGC) dendrites, synapses, and survival. Here, we tested the hypothesis that AMPK is an early mediator of metabolic stress in glaucoma.
Methods: Unilateral elevation of intraocular pressure was induced by injection of magnetic microbeads into the anterior chamber of mice expressing yellow fluorescent protein in RGCs. Inhibition of AMPK was achieved by administration of siRNA or compound C. RGC dendritic trees were 3D-reconstructed and analyzed with Imaris (Bitplane), and survival was assessed by counting Brn3a or RBPMS-labeled soma and axons in the optic nerve. RGC function was examined by quantification of anterograde axonal transport after intraocular administration of cholera toxin β-subunit. Retinas from glaucoma patients were analyzed for expression of active AMPK.
Results: Ocular hypertension triggered rapid upregulation of AMPK activity in RGCs concomitant with loss of mTORC1 function. AMPK inhibition with compound C or siRNA effectively restored mTORC1 activity and promoted an increase in total dendritic length, surface and complexity relative to control retinas. Attenuation of AMPK activity led to robust RGC soma and axon survival. For example, 95% of RGCs (2,983±258 RGCs/mm^2, mean ± S.E.M.) survived with compound C compared to 77% in vehicle-treated eyes (2,430±233 RGCs/mm^2) (ANOVA, $P<0.001$) at three weeks after glaucoma induction (n=8–10/group). Importantly, blockade of AMPK activity effectively restored anterograde axonal transport. Lastly, RGC-specific upregulation of AMPK activity was detected in human glaucomatous retinas relative to age-matched controls (n=10/group).
Conclusions: Metabolic stress in glaucoma involves AMPK activation and mTORC1 inhibition promoting early RGC dendritic pathology, dysfunction and neurodegeneration.

Keywords: Metabolic stress; retinal ganglion cell (RGC); adenosine monophosphate-activated protein kinase (AMPK); glaucoma

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