Implications of Sustained Elevation in Extracellular ATP in Retina Following Chronic Ocular Hypertension

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While short-term elevations in intraocular pressure (IOP) have been shown to increase the concentration of adenosine triphosphate (ATP) in ocular fluids and in the retina, effects of chronic IOP on ATP levels in the eye have not been examined. Using three different animal models of ocular hypertension, Lu et al.1 observed that ATP and the ectonucleotidase nucleoside triphosphate diphosphohydrolase-1 (NTPDase1) are both significantly elevated in eyes subjected to elevated IOP for extended periods of time. Intraocular pressure was elevated by ~10 mm Hg for 2 weeks in rats, by 3 to 4 mm Hg for 30 weeks in mice, and by 10 to 30 mm Hg for 15 weeks in monkeys. Interestingly, ATP levels in the vitreous increased 30-fold above control in rats, which experienced the shortest duration of ocular hypertension, compared to ~2.5-fold ATP elevation in the other two species.

Acutely, ATP release by cells is a homeostatic response to mechanical stimuli, such as occurs during transient IOP spikes. However, prolonged IOP elevations may be disruptive to purinergic signaling. The responses are complex, and while more work needs to be done to fully understand them, it appears that elevated ATP is balanced by upregulation of corresponding metabolic enzymes that convert extracellular ATP to adenosine. Levels of NTPDase1 increased in retinas of all eyes subjected to chronic IOP elevation in the present study. Unlike the detrimental impact of ATP binding to P2X7 receptors on retinal ganglion cells (RGCs), adenosine interactions with adenosine A1 and A3 receptors on RGCs are protective. It would be interesting to see the impact of prolonged elevation in IOP on RGCs in the presence or absence of antagonists to P2X7 versus A1/A3 receptors. In any case, the present study shows for the first time that ATP levels are sustained upon chronic elevation of IOP in three different animal models, implying a common mechanism by which purinergic signaling may in part contribute to RGC death in glaucoma.

Reference


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