Topical Administration of a ROCK/NET Inhibitor Promotes Retinal Ganglion Cell Survival and Axon Regeneration

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Purpose/Relevance
Intraocular pressure (IOP)-lowering ophthalmic solutions that inhibit Rho-associated protein kinases (ROCK) and norepinephrine transporters (NET) are currently under clinical evaluation. Here we evaluate topical application of one such drug for effects on retinal ganglion cell (RGC) survival and axon regeneration after optic nerve injury.

Methods
We performed optic nerve crush on young rats (P18) and topically applied Rock/Net inhibitor AR-13324 or placebo 3 times a day for 14 days. IOP was measured starting 3 days before and up to 9 days after injury. On day 12, cholera toxin B (CTB) was injected intravitreally to trace optic nerve regeneration. On day 14, retinas and optic nerves were collected. The retina was flat-mounted and stained with RBPMS to quantify RGC survival and the optic nerve was sectioned for optic nerve axon quantification using fluorescent and confocal microscopy. Rock phosphorylation targets implicated in axon growth including Cofilin and LIMK were examined by fluorescence microscopy and quantitative western blotting.

Results
AR-13324 lowered IOP as expected. RGC survival and optic nerve axon regeneration were significantly higher with Rock/Net inhibitor treatment compared to placebo. Furthermore, topical therapy decreased Rock target protein phosphorylation in the retina and proximal optic nerve.

Discussion
These data suggest that topical administration of a Rock/Net inhibitor promotes RGC survival and regeneration after optic nerve injury, with associated molecular changes indicative of posterior drug activity.

Conclusion
Coordinated IOP lowering and neuroprotective or regenerative effects may be advantageous in the treatment of patients with glaucoma.

Reference