SAVING THE OPTIC NERVE

STUDY IN BRIEF

- Intraorbital optic nerve crush is widely used to study factors that inhibit spontaneous retinal ganglion cell (RGC) axonal regeneration and potential interventions to promote regrowth and reinnervation of brain targets. Even so-called complete or total crush can spare some RGC axons, however, thereby confounding interpretation of the results.

WHY IT MATTERS

In addition to orbital and head trauma, glaucoma and other optic neuropathies assault RGC axons in the optic nerve. Because these axons are part of the central nervous system, once injured, their capacity for recovery is limited. Increasingly, investigators test therapeutic interventions for their ability to promote regeneration of lost axons in the optic nerve. As researchers’ understanding of the signals that inhibit neuronal growth increases, so do possibilities for leveraging this information clinically.
transection is an extremely difficult surgery to perform in the small postorbital space of the mouse.

To gauge the extent of initial damage, Fischer and colleagues recommended the use of neurochemical surrogates, particularly markers for astroglia processes, which can reach across the injury site. Identifying specific markers for a newly generated axon would also distinguish regenerating from spared axons.

Finally, improved in vivo optical imaging to track recovery of damaged optic nerve axons might eliminate some of the post hoc inference necessary in current acute approaches to regeneration.

ASTROCYTE-DERIVED LIPOXINS A₄ AND B₄ PROMOTE NEUROPROTECTION FROM ACUTE AND CHRONIC INJURY

Livne-Bar I, Wei J, Liu HH, et al²

ABSTRACT SUMMARY

This laboratory investigation explored a prosurvival relationship between retinal astrocyte glia and RGCs challenged by disease-relevant stressors in experimental models. Astrocytes distribute densely across the retinal nerve fiber layer, forming intimate connections with both RGC axons and retinal vasculature. Astrocytes also provide metabolic and other support to RGC axons in the optic nerve. Livne-Bar and colleagues probed how small lipid mediators called lipoxins (LXA₄ and LXB₄) derived from isolated retinal astrocyte secretions influence the survival of RGCs challenged by acute injury (kainic acid injection to the eye) and by chronic glaucomatous insult (elevated IOP via circumlimbal suture). Lipoxins are members of a superfamily of small polyunsaturated fatty acid-derived metabolites with known anti-inflammatory properties.

The investigators found that LXA₄ and LXB₄ delivered via intravitreal injection or via a combination of intraperitoneal and topical application provided structural and functional neuroprotection to RGCs in their injury models.

DISCUSSION

Are astrocytes important mediators of neuronal survival?

In the canonical view, astrocyte signals in eye disease have a proinflammatory, proapoptotic, late role in pathogenesis known collectively as reactive gliosis. By maintaining glutamate homeostasis, supplying antioxidants, and providing metabolic support for neuronal signaling between the retina and brain, however, astrocytes support normal axonal function. A high degree of astrocyte remodeling prior to frank degeneration in glaucoma suggests that the cells play a more complex role in pathogenesis, one likely involving modulation of these key physiologic elements to preserve axonal function for as long as possible.

As Livne-Bar and colleagues noted, neurodegeneration involves a combination of the induction of neuroinflammatory signals and a concordant loss of homeostatic prosurvival cues. Importantly, the investigators demonstrated diminished LXA₄ and LXB₄ activity in the retina in response to injury. Because treatment improves RGC survival, this finding indicates an important role for astrocyte-derived lipoxin signaling in normal function.

What are the implications for clinical care?

Livne-Bar and colleagues emphasized that dysregulation of lipid mediators is implicated in a variety of age-related diseases, including Alzheimer disease, stroke, and age-related macular degeneration. Their study presented the first evidence, however, that astrocyte-derived lipoxins have a directly neuroprotective role. Furthermore, the researchers proposed a plausible mechanism of action involving modulation of signaling via immune-derived tumor necrosis factor α, a proinflammatory cytokine implicated in neurodegenerative injury. Although there is general consensus that astrocytes in the...
optic nerve head influence the early axonopathy that characterizes glaucoma, this study suggested that retinal astrocytes may be equally important in regulating RGC survival. If that idea proves to be accurate, the pursuit of a topical treatment that protects RGCs independent of IOP may become both mechanistically and clinically feasible.


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