Neuroprotective effects of transcription factor Brn3b in an ocular hypertension rat model of glaucoma

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PURPOSE: Glaucoma is an optic neuropathy commonly associated with elevated intraocular pressure (IOP), leading to optic nerve head (ONH) cupping, axon loss and apoptosis of retinal ganglion cells (RGCs) which could ultimately result in blindness. Brn3b is a class-4 POU domain transcription factor that plays a key role in RGC development, axon outgrowth and pathfinding. Previous studies suggest that a decrease in Brn3b levels occurs in animal models of glaucoma. The goal of this study was to determine if adeno-associated virus (AAV)-directed overexpression of the Brn3b protein could have neuroprotective effects following elevated IOP-mediated neurodegeneration.

METHODS: IOP was elevated in one eye of Brown Norway rats (Rattus norvegicus), following which the IOP-elevated eyes were intravitreally injected with AAV constructs encoding either the GFP (rAAV-CMV-GFP and rAAV-hsyn-GFP) or Brn3b (rAAV-CMV-Brn3b and rAAV-hsyn-Brn3b). Retina sections through the ONH were stained for synaptic plasticity markers and neuroprotection was assessed by RGC counts and visual acuity tests.

RESULTS: AAV-mediated expression of the Brn3b protein in IOP-elevated rat eyes promoted an upregulation of growth associated protein-43 (GAP-43), actin binding LIM protein (ablIM) and acetylated α-tubulin (ac-Tuba), both posterior to the ONH and in RGCs. The RGC survival as well as axon integrity score were significantly improved in IOP-elevated rAAV-hsyn-Brn3b injected rats compared to those of the IOP-elevated rAAV-hsyn-GFP injected rats. Additionally, intravitreal rAAV-hsyn-Brn3b administration significantly restored the visual optomotor response in IOP-elevated rat eyes.

CONCLUSION: AAV-mediated Brn3b protein expression may be a suitable approach for promoting neuroprotection in animal models of glaucoma.