Regeneration of retinal ganglion cell dendrites: the role of insulin signaling to stimulate connections and restore vision in glaucoma.

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INTRODUCTION: Loss of vision in glaucoma results from the irreversible death of retinal ganglion cells (RGCs). The dendrites of RGCs are the substrate for receiving synaptic inputs. The structural stability of dendritic arbors is, therefore, essential for the normal function of RGCs and their ability to transmit visual information. The rapid retraction of RGC dendrites and loss of synapses is one of the earliest pathological features of ocular hypertension damage. A crucial step towards circuit repair in glaucoma is to promote damaged RGCs to regenerate not only axons, but also dendrites to successfully reconnnect with their synaptic partners. Paradoxically, although much is known about axonal regeneration, the capacity of injured RGCs to re-generate dendrites has been largely ignored.

HYPOTHESIS: Here, we tested the hypothesis that insulin will stimulate dendrite regeneration and re-establishment of synaptic connections thus improving survival and function in injured RGCs.

SPECIFIC AIDS

Aim 1: Characterize the role of insulin on RGC dendrite regeneration and survival after axonal injury.

Aim 2: Determine the efficacy of insulin to regenerate RGC synapses and promote functional recovery.

METHODS

Glaucoma model and axotomy: Ocular hypertension was induced by intracameral injection of magnetic microbeads in Thy1-YFP mice followed by intracranial pressure measurements as described by us. Axotomy was performed by exposing the optic nerve (ON), which was cleanly transected at 0.5-1 mm from the ON head. Care was taken not to damage the central retinal artery, and fundus examination was routinely performed before and after the procedure to verify the integrity of the retinal circulation.

Insulin administration: Human recombinant insulin diluted in sterile, endotoxin free PBS (15-300 μg/kg/day) was administered by daily intraperitoneal (i.p.) injections or eye drops (5 μl drop) as per the regimens outlined here.

RESULTS

1. Insulin promotes dendrite regeneration

2. Synaptic density is restored by insulin

3. Insulin rescues retinal function

4. Neuronal survival is robustly increased

CONCLUSIONS

Our study reveals that adult RGCs are endowed with the ability to effectively regenerate dendrites and synapses once they have been lost. Importantly, we identify insulin as a powerful strategy to restore dendritic morphology and enhance the function and survival of RGCs after acute optic nerve injury and in experimental glaucoma.

IMPACT FOR GLAUCOMA PATIENTS

The relevance of our observation that insulin eye drops exert a potent pro-regenerative effect is reinforced by findings that insulin applied at doses as high as 100 μU/ml, several-fold higher than those tested in our experiments, were innocuous and produced no detectable clinical toxicity when applied topically (on the cornea) in humans. Collectively, our data support the rationale for using insulin and its analogues as pro-regenerative therapeutic targets to counter progressive RGC neurodegeneration and vision loss in glaucoma.

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