Chemokine receptor antagonist as a new treatment of ocular hypertension and subsequent retinal degeneration in a rat model of glaucoma.

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We previously reported that the chemokine receptor CXCR3 is involved in the regulation of trabecular cell viability in vitro [1]. In the present work, we tested in a rat model of glaucoma the effects of a CXCR3 antagonist on the intraocular pressure, filtering function of the trabecular meshwork, and on related retinal neurodegeneration.

1- In vivo antagonism of CXCR3 lowers the intraocular pressure

Intraocular pressure was significantly decreased during 6 weeks in hypertensive eyes treated with a CXCR3 antagonist as compared to untreated hypertensive eyes. n=10 in each group, P< 0.01 for each measure.

2- In vivo antagonism of CXCR3 prevents retinal degeneration and protects the visual function

A: Decrease in retinal nerve fiber density observed in untreated glaucoma eye was counteracted by CXCR3 antagonist (in vivo scanning laser ophthalmoscopy). B: Visual function in rats was also preserved in glaucomatous eyes receiving CXCR3 antagonist compared to untreated glaucoma eyes as assessed by optokinetic testing, n=10 in each group, ** and §§ P<0.01.

3- In vivo antagonism of CXCR3 restores the trabecular filtering function

A: Decrease in aqueous humor outflow observed in glaucoma eyes was counteracted by CXCR3 antagonist as compared to untreated eyes. B: Percent of effective filtration length (PEFL) in the trabeculum was also restored by CXCR3 antagonist (trabecular trapping of fluorescent microspheres quantified by confocal microscopy in flat-mounted anterior segments). C: CXCR3 antagonism in glaucoma eyes protected trabecular cells against apoptosis as compared to untreated eyes (TUNEL [green] and DAPI [blue] in eye cryosections). n=10 in each group, ** P< 0.01; scale bar = 50 µm

We demonstrate that ocular administration of a non-peptide selective antagonist of CXCR3 lowers intraocular pressure by restoring the trabecular filtering function, further providing retinal neuroprotection in a rat model of glaucoma. This innovative strategy opens new therapeutic avenues based on chemokine/chemokine receptor targeting in this major ocular disease.

METHODS

Animal model: Epidural vein cannulation was performed in one eye of male Long-Evans rats in order to obtain stable increase in intraocular pressure [2]. Two subconjunctival injections of a non-peptide selective antagonist of CXCR3 (ANT7420, 10 µM, L. L. III) were done one month after the treatment.

CPU and Trabecular Filtering Function: Intraocular pressure was measured weekly using a hand-held tonometer. Aqueous humor outflow was evaluated in vivo by fluorophotometry [4] and the trabecular/Draining function was quantified using intracameral injection of fluorescent microspheres and confocal imaging in flat-mounted anterior segments [5]. Density of apoptotic cells was counted in eye cryosections using TUNEL.

Retinal Morphology and Function: Retinal nerve fibers were counted in vivo using scanning laser ophthalmoscopy. Visual function was assessed by optokinetic testing [6].

REFERENCES