Jules Stein Eye Institute
U C L A

Clinical Update

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Self-Defense Against Glaucoma?

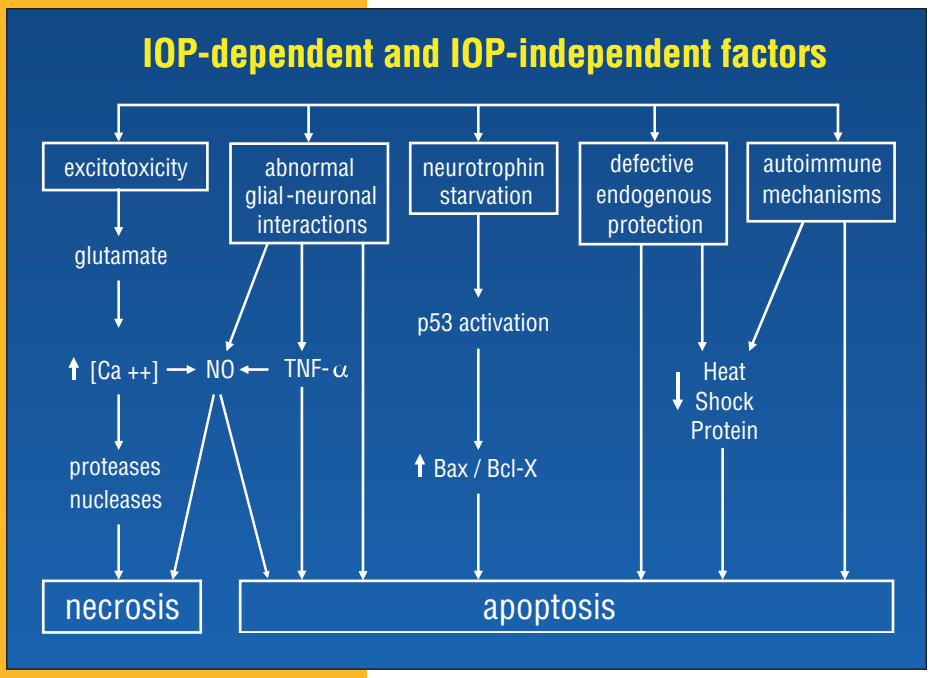

Figure 1: Schematic of the potential pathways for neuroprotection of retinal ganglion cells against glaucomatous damage.

Hope for patients with progressive glaucoma may lie, in essence, within, according to Joseph Caprioli, M.D., Stark Professor of Ophthalmology and Chief of the Glaucoma Division at the Jules Stein Eye Institute. "Lowering intraocular pressure by medication or surgery fails to help many patients and probably doesn't address underlying mechanisms of optic nerve damage. Enhancing endogenous self-defense mechanisms to directly safeguard the optic nerve would be a more comprehensive way to manage glaucoma. Our focus now is on neuroprotective strategies as a means of sustaining the optic nerve that have significant clinical potential," he says.

In Principle

Manipulating and mitigating destructive physiologic processes — via calcium channel blockade, glutamate blockade, antioxidants, nitric oxide synthase inhibition, anti-apoptotic pathways, cellular regeneration, and particularly stress protein induction — are approaches that engage much ongoing research, including Dr. Caprioli's. He believes the concept of rousing the body's own protective mechanisms to withstand disease is quite realistic. Citing Nietzsche's axiom, "What does not destroy me makes me stronger," Dr. Caprioli explains, "Sublethal stressors actually boost the body's own healing mechanisms, which are among the fundamental processes that occur in all living cells. The genetic code for the stress proteins, for instance, is highly homologous between bacteria and humans. Investigations of various agents and mechanisms that stimulate endogenous protection are promising, and species specificity is unlikely to be a problem." (Figure 1)

Precedents and Possibilities

One precedent for this approach that exploits endogenous neuroprotection clinically, says Dr. Caprioli, is the anti-ulcer agent geranylgeranylacetone (GGA) being used successfully for patients in Japan. "An oral regimen of GGA protects the gastric mucosa without affecting gastric acid or pepsin secretion. It has also been effective and nontoxic for other organ systems, including the liver, lung, kidney, and heart, and has been shown to penetrate the central nervous system," he notes. "Recently, our own studies in an animal model confirmed GGA to be neuroprotective in the eye as well: pretreatment with GGA induced heat shock protein (HSP72) expression, thereby protecting retinal ganglion cells from glaucoma

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GLAUCOMA

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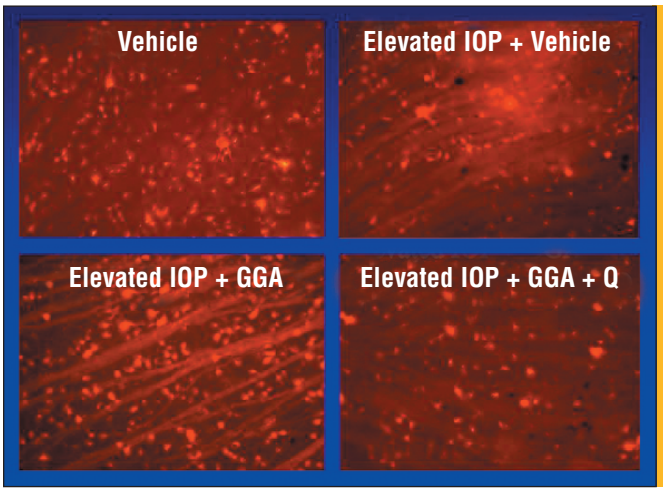

Figure 2: Flat mounts of retinal ganglion cells (RGCs) in a rat model of glaucoma. Top left, control. Top right, the decreased number of RGCs after exposure to elevated IOP for 8 weeks. Bottom left, the protective effect of adding GGA: the RGC counts are similar to controls, GGA having blocked the glaucomatous damage. Bottom right, shows the effect of quercetin (Q), which abolishes the protective effects of stress (heat-shock) proteins.

damage." Furthermore, says Dr. Caprioli, there were no signs of side effects or toxicity after repeat GGA administration, a significant factor if it is to be used for ongoing treatment in glaucoma patients. (Figure 2)

Another neuroprotective agent, the glutamate blocker Memantine, may be even closer to application in a clinical setting. "Memantine has proven beneficial for patients with Alzheimer's disease," Dr. Caprioli states. "Currently, Jules Stein Eye Institute is participating in a multi-center clinical trial using Memantine as an adjunct to intraocular pressure control, assessing its effectiveness in optic nerve neuroprotection and its potential for patients with glaucoma."

Next Questions

Demonstrating the efficacy of heat shock protein induction and other neuroprotective mechanisms brings treatment possibilities closer, but many issues of clinical feasibility — dosage, timing, tolerance — remain to be investigated further. Dr. Caprioli notes that, in laboratory studies, increased production of neuroprotective stress proteins is fairly transient, peaking at 12 hours after challenge and falling again after 24 to 36 hours. How, then, can stress protein induction be used to treat a chronic disease occurring over years? He says, "Perhaps some sort of pulsed treatment — repeated induction of the stress proteins — would be the key. The usefulness of GGA in ulcer patients proves that this general approach does work for a chronic disease. I would hope that whatever neuroprotective stimulant we develop could be used once a day or once a week, which is the way many drugs work."

Other "Home" Remedies?

In addition to the potential of medication therapies, Dr. Caprioli believes that there may be other, non-drug means for enhancing endogenous protection, such as hyperthermia. "Interestingly, medical history before antibiotics records a 'fever treatment' using toxins to cause high fever for a brief time to help some patients with tuberculosis and other diseases. Induction of stress protein may explain the observed benefits of that approach," he says. Similarly, recent oncology literature reports that patients receiving bone marrow transplants who became septic and developed high fever had a lower recurrence rate of their cancers than those patients who never developed fever. "Perhaps raising body temperature, even through intense exercise or taking a sauna periodically, could someday be used to enhance neuroprotection enough to defend against glaucoma and other neurodegenerations," he notes.

Dr. Caprioli and his colleagues at the Institute have also been pursuing and are about to publish findings about whether caloric restriction provides enough subtle stress on the body, without harming health, to protect against certain diseases including ocular disorders. Barring unforeseen roadblocks, he anticipates clinical trials within a few years to study these non-drug approaches as well as medical means of self-activating neuroprotection.

In Practice

Developing a neuroprotective approach to glaucoma, says Dr. Caprioli, would be particularly beneficial for those patients with so-called normal tension glaucoma, in whom nerve damage progresses despite treatments to lower intraocular pressure. "Since glaucoma is probably a spectrum of diseases, having in common a characteristic optic nerve damage associated with a characteristic course of visual loss, I favor the endogenous protective approach most. It is likely to be effective for different mechanisms of damage, and we won't need to know the exact mechanism for it to work," he notes. Decreasing the cell's susceptibility to damage and death across a wide range of insults would be a real advantage and has much broader potential than current therapies."

PUBLICATIONS:

Park KH, Cozier, F, Ong OC, *Caprioli J: Induction of heat shock protein 72 protects retinal ganglion cells in a rat glaucoma model.* Invest Ophthalmol Vis Sci 2001; 42:1522-30.

Ishii Y, Kwong JKM, *Caprioli J: Retinal Ganglion Cell Protection with Geranylgeranylacetone, a Heat Shock Protein Inducer, in a Rat Glaucoma Model.* Invest Ophthalmol Vis Sci 2003; 44: 1982-92.

Ophthalmology Clinical Laboratories

The Ophthalmology Clinical Laboratories at the Jules Stein Eye Institute provide precise measurements, photographs, and quantitative studies of the eye and the visual system. Services include fluorescein angiography, glaucoma testing, ocular motility testing, ophthalmic photography, ultrasonography, visual field testing and visual physiology. Laboratory services are available to referring ophthalmologists in the community.

Glaucoma Photography Laboratory

The Glaucoma Photography Laboratory provides a series of specialized photographs to assist in the management of new and follow-up glaucoma patients. Heidelberg retinal tomography (HRT II), using confocal laser light, measures structural parameters of the optic nerve and provides more information on the nerve fiber layer. The Nerve Fiber Analyzer (GDx Access VCC) uses polarized light in place of dilation to measure the thickness of the nerve fiber layer and is particularly useful in diagnosing new glaucoma. Optical coherence tomography (OCT Stratus) uses measurements of reflected light to measure the nerve fiber layer as well as to measure macular holes as a staging procedure for surgical repair, and detecting cystoid macular. An ophthalmic fundus camera photographs the optic nerve in stereo.

Director: *Joseph Caprioli, M.D.*
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Ocular Motility Clinical Laboratory

The Ocular Motility Clinical Laboratory records and quantitatively analyzes eye movement abnormalities resulting from ocular and neurological disorders, such as ocular myasthenia gravis. Four types of tests are performed. Electro-oculography (placing electrodes around the eye) evaluates nerve muscle palsies and lost or slipped eye muscles. The Hess screen test evaluates patterns of strabismus in patients who are able to perceive diplopia. Magnetic scleral search coil techniques are utilized in clinical research studies for maximum resolution of vertical as well as horizontal eye movements. Video recording of eye and eyelid movement is also performed.

Director: *Joseph L. Demer, M.D., Ph.D.*
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(310) 206-6354

Ophthalmic Photography Laboratory

The Ophthalmic Photography Laboratory provides a wide array of clinical examination techniques to aid in the diagnosis and management of complex eye conditions. Patient care services in the laboratory include photographic documentation of anterior segment diseases; photographs of ocular motility to record abnormalities of eye movement; fundus photography; and diagnostic testing using fluorescein and indocyanine green angiography, which record the dynamics of blood flow in the eye. The laboratory also supports the research and teaching activities of the Jules Stein Eye Institute by preparing and duplicating graphic materials for presentation and publication.

Director: *Steven D. Schwartz, M.D.*
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(310) 825-6398

Ophthalmic Ultrasonography Laboratory

The Ophthalmic Ultrasonography Laboratory performs clinical examinations that are useful in diagnosing ocular and orbital eye diseases and performing intracocular lens calculation for cataract surgery. Standardized A-scan ultrasonography is useful in tissue differentiation and is employed to diagnose ocular and orbital tumors. Biometry and lens calculation examinations are performed to determine the power of the lens implant for cataract patients. B-scan ultrasonography provides tumor and foreign body location and contour information. Ultrasound biomicroscopy provides detailed, high-resolution views of the anterior segment of the eye and is a critical tool for the evaluation of ocular pathology, including choroidal melanoma and involvement of lens, iris and ciliary body. Optical coherence tomography (OCT 3) uses the most advanced technology to image a cross-section of the retinal contour and is especially helpful in visualizing retinal lesions that affect the retinal cyto-architecture and vitreoretinal interface.

Director: *Marc O. Yoshizumi, M.D.*
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Ophthalmology Diagnostic Laboratory

The Ophthalmology Diagnostic Laboratory offers four quantitative tests, including measurement of vision acuity and field of vision. The potential acuity meter (PAM) and the laser interferometer measure potential vision acuity, usually preparatory to cataract surgery, for

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CLINICAL LABORATORY SERVICES

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patients with complicating eye diseases such as macular degeneration. The Goldmann perimeter uses manual perimetry to measure the field of vision (including peripheral vision). This is particularly useful for patients such as those with retinal degenerations who cannot perform automated perimetry. The endothelial cell counter uses a high-powered microscope and video camera to photograph the inner layer of the cornea and measure corneal thickness.

Director: *Joseph Caprioli, M.D.*
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(310) 825-5798

Visual Field Laboratory

The Visual Field Laboratory performs visual field examinations that determine the sensitivity of central and peripheral vision. Examinations are conducted with Humphrey automated perimetry equipment. Testing detects visual field deficits associated with glaucoma, retinal disorders, and neuro-ophthalmic conditions. Utilizing pinpoints of light that are projected around a perimetry bowl, the test evaluates different areas of the field of vision. Test results are computerized and compared to a range of normal values by age group. Patterns of diminished fields of vision are related to specific eye diseases. Perimetry testing is employed for diagnostic purposes and to monitor visual field sensitivity over time, especially for glaucoma patients. Both standard and shortwave-length automated techniques are available in addition to frequency-doubling perimetry (FDT) and motion detection perimetry.

Director: *Joseph Caprioli, M.D.*
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Visual Physiology Laboratory

The Visual Physiology Laboratory evaluates the function of the retina and visual pathways to confirm a specific diagnosis or rule out alternative diagnostic possibilities. Electrophysiological tests, including the full-field electroretinogram (ERG) and multifocal electroretinograms (MERG), electro-oculogram (EOG), and visually evoked cortical response (VECR), record electrical signals generated from different layers of the visual system. Psychophysical tests require the participation of the patient in specific tasks to evaluate visual function. The Visual Physiology Laboratory performs color discrimination testing, contrast sensitivity testing and threshold dark adaptometry. In many cases, both electrophysiological and psychophysical tests are performed together in order to obtain a specific diagnosis.

Directors: *John R. Heckenlively, M.D. and Steven Nusinowitz, Ph.D.*
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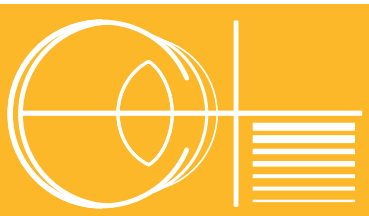

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