De-stressing glaucoma

By Benjamin Boettner, Associate Editor

Glucocorticoids are standard of care for a host of allergic and inflammatory eye conditions, but they elevate intraocular pressure about a third of the time and can result in secondary open-angle glaucoma. A chemical chaperone called sodium phenylbutyrate could eliminate that side effect, according to new research from **The University of Iowa**.[1]

The findings may hand a new indication to two companies—one Swedish, one Canadian—that market oral versions of phenylbutyrate (PBA) for other diseases.

Glaucomas develop when aqueous fluid that enters the eye via the ciliary body is not effectively drained through structures including the trabecular meshwork. This leads to elevated intraocular pressure (IOP) and causes progressive degeneration of retinal ganglion cells and damage to the optic nerve. The ultimate result is visual field loss and blindness.

Primary open-angle glaucoma is the most common type and results from progressive increases in intraocular pressure that damage the optic nerve.[2] Primary glaucoma typically is treated with latanoprost, a generic prostaglandin F receptor (PTGFR) agonist.

Other drugs to treat primary open-angle glaucoma include **Allergan Inc.**'s adrenergic receptor α_2 (ADRA2) agonist Alphagan P brimonidine and Latisse bimatoprost, a prostaglandin F analog. **Merck & Co. Inc.** sells the adrenergic receptor β (ADRB) blocker Timoptic timolol.

There are no drugs specifically approved for secondary open-angle glaucoma including glucocorticoid-induced glaucoma. In addition, it is unclear why glucocorticoids cause the condition.

"The clinical standard for treating glucocorticoid-induced glaucoma is to either take patients off steroids or switch them to less potent ones. Being able to specifically lower the steroid-mediated rise in IOP could allow continued glucocorticoid treatments and improve overall therapeutic outcome in many patients," said Val Sheffield, a professor in the Department of Pediatrics at the University of Iowa and a **Howard Hughes Medical Institute** investigator.

Now, Sheffield's group has pinpointed a stress response in the endoplasmic reticulum (ER) as the root of glucocorticoid-induced glaucoma formation. To combat the problem, the researchers used PBA, which they previously showed alleviated ER stress in a mouse model of genetically linked glaucoma.[3]

The first step was generating a mouse model in which topical ocular administration of the glucocorticoid dexamethasone mimicked the loss of retinal ganglion cells, optic nerve damage and IOP that occur in primary glaucoma.

In cultured human trabecular meshwork cells and in the mice, ER stress markers were reversibly upregulated by dexamethasone. In mice with dexamethasone-triggered IOP, deletion of an ER stress regulator called DNA-damage-inducible transcript 3 (Ddit3; Chop10; Chop; Gadd153) or systemic administration of PBA significantly lowered IOP and expression of ER stress markers compared with wild-type Chop expression or vehicle administration.

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The group was led by Sheffield and Gulab Zode, who now is an assistant professor in the Department of Cell Biology and Immunology at the **University of North Texas Health Science Center**.

The results were published in *The Journal of Clinical Investigation*.

"The finding that suppression of ER stress by PBA, an existing drug, can prevent the glaucoma response to steroids is important and presents an unexplored avenue," said Joel Schuman, director of the **University of Pittsburgh Medical Center**'s Eye Center and a professor of clinical and translational sciences at the **University of Pittsburgh School of Medicine**.

Formulating PBA

Sheffield said that his group is going to collaborate with the Department of Ophthalmology at the University of Iowa to test whether PBA can prevent IOP elevation in patients treated with glucocorticoids. "Our plan is to formulate a PBA eye drop, but the details are not in place at this time," he said.

PBA is marketed by **Swedish Orphan Biovitrum AB** as Ammonaps sodium phenylbutyrate in an oral formulation to treat urea cycle disorder. **Valeant Pharmaceuticals International Inc.** sells an orally available desalted glycerol derivative called HPN-100 for the indication. Neither company returned calls for comment.

Schuman and Robert Weinreb both said that a new formulation of PBA—preferably for local delivery to the eye—is needed for the new ophthalmic indication.

"This could minimize systemic side effects. Local administration of PBA via eye drop or, alternatively, long-acting intracameral injection—if safe—does seem reasonable," said Weinreb, a distinguished professor and director of the Shiley Eye Center at the **University of California, San Diego**.

Weinreb and Jonathan Lin, an associate professor in the Department of Pathology and Department of Ophthalmology at the **University of California, San Diego School of Medicine**, wanted to see a more refined picture of what happens when glucocorticoids upregulate ER stress.

"Studies of aqueous dynamics to sort out whether the increased pressure is solely related to increased outflow resistance in the trabecular meshwork or also changes in the ciliary body would be of interest," said Weinreb.

Lin said that it would be "interesting to find out if misfolded proteins indeed accumulate on the anatomical level and how glucocorticoids and other triggers exactly cause the ER stress. Investigating the response

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—Val Sheffield, The University of Iowa

in knockout situations for other ER stress genes could provide a way to test for specific requirements and work out which parts of the ER stress response confer the pathogenic effects."

Lin is investigating how the unfolded protein response senses ER stress in diseases involving retinal degeneration.

Schuman said that one approach could be to manipulate human primary trabecular meshwork cells and human organ cultures in which eyes obtained from cadavers are perfused and treated with molecules that induce or manipulate the ER stress response.

Stefan Marciniak said that given the benefits of *Chop* gene deletion in the mouse model of glaucoma, it would make sense to attempt to target eukaryotic translation initiation factor 2α kinase 3 (EIF2AK3; PERK), which functions upstream of Chop activation. He suggested that local application of PERK inhibitors to the eye could circumvent the side effects of systemic versions.

Marciniak is a senior clinical research fellow at the **Medical Research Council** based at the **Cambridge Institute for Medical Research**. He studies the unfolded protein response in pulmonary and other diseases.

Playing chaperone

In the longer term, Sheffield's group wants to use PBA more broadly in primary glaucoma.

"If steroids promote increased flux of proteins through the secretory pathway to cause ER stress, and this would be more common in glaucoma, then ER stress–directed treatments might have broader benefits in this condition," said Marciniak.

Sheffield said, "We believe that ER stress is not limited to glucocorticoid glaucoma. Currently, we are studying the involvement of ER stress in general primary glaucoma. We are also planning to conduct a clinical study on primary open-angle glaucoma–associated ER stress–causing mutations to test whether PBA can reduce elevated IOP in these patients."

The findings have not been patented.

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COMPANIES AND INSTITUTIONS MENTIONED

Allergan Inc. (NYSE:AGN), Irvine, Calif.
Cambridge Institute for Medical Research, Cambridge, U.K.
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