MYELINATION TRANSITION ZONE
ASTROCYTES ARE CONSTITUTIVELY
PHAGOCYTIC AND HAVE SYNUCLEIN
DEPENDENT REACTIVITY IN GLAUCOMA
Nguyen JV, Soto I, Kim KY, et al*
Proceedings of the National Academy of Sciences, January 2011

This article identified a new degradation pathway that might be responsible for the axonal degeneration we see in glaucoma. This mechanism matches the characteristic pattern of glaucomatous damage, reflects an ability to be modulated by IOP increases, and has inborn genetic variability.

Supportive Astrocytes Gone Wild
Optic nerve head (ONH) astrocytes are capable of phagocytosis and do not have a purely supportive function. Nguyen et al demonstrated that astrocytes in healthy mice have a constitutive expression of Mac-2, a “clean-up” gene, which is normally only present in specialized phagocytic cells. There was histological evidence of destruction of the ONH, with ingested portions of neuronal axons found inside astrocytic cells. The expression of Mac-2 and largest cellular fragments were primarily found in a specific area of the retro-laminar ONH where myelination of the optic nerve begins. This so-called myelin transition zone has constitutive internalization of axonal material, whereas the surrounding cells only become phagocytic after damage to the nerve has occurred. The authors pointed out that the unique properties of this anatomic location could lead to the striking arcuate pattern of damage that is typical for retinal nerve fiber loss in glaucoma.

Increased IOP Causes Astrocytes to Digest the Optic Nerve
The authors found that increased IOP caused astrocytes outside the myelin transition zone to become phagocytic through increased Mac-2 expression. This provides a plausible mechanism by which glaucomatous damage could begin during a patient’s lifetime and would fit with our knowledge that lowering IOP with medication/surgery is an effective way to reduce glaucomatous progression. Remarkably, this change in gene expression was specific to pressure increase and did not occur with other manipulations of the nerve (eg, optic nerve crush).

Genetic Variation in Astrocyte Phagocytosis due to Gamma Synuclein
These results suggest that failure to clear axon-derived material (one of them being gamma synuclein) at the myelin transition zone may contribute to axonal loss in glaucoma. The findings indicate that there are protease-resistant forms of gamma synuclein in glaucoma that are similar to Parkinson disease. There are different types and amounts of gamma synuclein; the DBA/2J glaucoma mouse model has a large amount of digestion-resistant gamma synuclein when compared with control mice.

Discovering the genetic and molecular triggers for glaucomatous damage has inherent appeal. The ability to modulate these triggers could lead to a very effective new class of medications that would treat the neuronal damage itself instead of a risk factor.

*Financial disclosures: The authors stated that they hold no proprietary interest in the materials discussed herein.

DIURNAL AND NOCTURNAL EFFECTS OF BRIMONIDINE MONOTHERAPY ON INTRAOCULAR PRESSURE
Liu JH, Medeiros FA, Slight JR, Weinreb RN*
Ophthalmology, November 2011

This study looked at the 24-hour pressure-lowering effect of brimonidine, which was especially interesting given that brimonidine is known to work through two mechanisms, reducing aqueous humor production and increasing uveoscleral outflow. Other medications that reduce aqueous humor production such as ß-blockers have been found to be ineffective at reducing IOP overnight, whereas prostaglandin analogues, which increase uveoscleral outflow, have been found to reduce IOP throughout the day and night.3,4

Brimonidine Does Not Lower IOP at Night
The authors showed that brimonidine monotherapy lowered IOP effectively during daytime hours but not during the night. The study recruited 40- to 70-year-old, newly diagnosed, untreated glaucoma or ocular hypertensive patients. Each patient received baseline 24-hour IOP measurements followed by a second 24-hour series after 1 month of treatment with brimonidine three times a day. Interestingly, this reduction in IOP after treatment could
be observed even when it was measured while patients were in the supine position during the day, showing that simple postural changes were not responsible. Heart rate, mean arterial pressure, and ocular perfusion pressure were measured before and after brimonidine treatment to ensure that topical brimonidine treatment did not affect these cardiovascular factors. In addition, the study was administered under strict laboratory conditions, with regulated hours of light and dark and monitored administration of eye drops at set 8-hour intervals.

**Use Brimonidine Only Before Breakfast and Lunch**

The authors stated that there is a plausible physiological rationale to explain the daytime-only IOP-reducing effects of brimonidine as well as β-blockers. Both classes of drugs act to suppress the endogenous β-adrenergic stimulus to produce aqueous that is only present during the daytime. Blocking this signal when it is not present, whether at the presynaptic α2 receptor or at the postsynaptic β receptor, does not lead to an appreciable change. It remains unknown why increases in uveoscleral outflow were not appreciable at night with brimonidine therapy as opposed to prostaglandin agonist therapy. The authors pointed out that, because brimonidine does not lower IOP during nighttime hours, the third dose of brimonidine taken at bedtime is unnecessary, adds to the cost, and reduces rates of compliance.

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**A RANDOMIZED TRIAL OF BRIMONIDINE VERSUS TIMOLOL IN PRESERVING VISUAL FUNCTION: RESULTS FROM THE LOW-PRESSURE GLAUCOMA TREATMENT STUDY**

Krupin T, Liebman JM, Greenfield DS, et al*

*American Journal of Ophthalmology, April 2011*

This study followed patients with primary open-angle glaucoma in the low pressure range. They were measured during daytime visits. Twice-daily treatments with an α-agonist, brimonidine, were compared to an inexpensive and widespread β-blocker, timolol. The different outcomes spur discussion of postulated secondary mechanisms (neuroprotection) and side effects (reduced perfusion) and may require many to rethink their prescribing practice.

**Brimonidine but Not Timolol Prevents Progression in Low-Pressure Glaucoma**

Patients with low-pressure glaucoma were randomly assigned to twice-daily monotherapy with either brimonidine tartrate 0.2% or timolol maleate 0.5%. They were observed for 4 years to detect visual field progression shown by a decrease of greater than 1 dB per year in the same three or more points showed on three consecutive tests. Subjects and physicians were blind to the medication assigned. Subjects were assigned in blocks of seven such that four patients received brimonidine and three received timolol, since the discontinuation rate for brimonidine is generally greater than that for timolol. Ninety-nine patients were randomized to brimonidine, and 79 were randomized to timolol.

Significantly fewer subjects treated with brimonidine (nine subjects, 9.1%) were found to have progressed than those treated with timolol (31 subjects, 28.3%) at the endpoint of the study, despite similar IOP values at all time points. A greater percentage of subjects assigned to brimonidine (28 subjects, 28.3%) withdrew from the study than patients assigned to timolol (nine subjects, 11.4%). The most common reason for withdrawal was localized ocular allergy, which occurred in 20 patients using brimonidine and three patients using timolol. Careful analyses were performed to ensure that there was no significant difference in the patients who discontinued treatment as opposed to subjects who remained in the study to ensure that the difference seen between treatment groups was not due to self-selection bias.

**Brimonidine Neuroprotection or Damaging Reduction of Perfusion With Timolol?**

Since brimonidine and timolol have very similar IOP-lowering profiles, this study provides an opportunity to evaluate the potential neuroprotective properties of the former. A little-known fact is that β-adrenergic receptor blockage (timolol) and α2 adrenergic receptor stimulation (brimonidine) have the same intracellular cascade, because both cause a downregulation of adenylate cyclase with decreased cyclic adenosine monophosphate. The fewer progressors in the brimonidine group could be due to protection conferred by brimonidine, a risk conferred by timolol, or some combination of the two.

A lowering in heart rate or blood pressure by timolol is one potential source of the greater progression amongst timolol recipients. A recent study by Quaranta et al, however, showed that treatment with brimonidine caused a greater decrease in these parameters than treatment with timolol.6 Pressure differences not captured during office visits are another potential source of this difference. Liu et al, however, indicated that brimonidine does not effectively lower IOP during the nocturnal period in primary open-
angle glaucoma patients; neither does timolol. A final explanation would relate to the different mechanisms of action of brimonidine and timolol, as brimonidine affects uveoscleral outflow in addition to aqueous production.

This well-conducted study lends support to the idea of a neuroprotective effect of brimonidine. The patients treated with this medication had less visual field loss despite similar daytime IOP values throughout the study period, with no other simple explanation for this effect. Critics of neuroprotective eye drops for humans had pointed in the past to the much larger diffusion distance in human eyes when compared with the much shorter distance in rodent eyes where neuroprotection can be demonstrated. 

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