

News in Review

COMMENTARY AND PERSPECTIVE

Surprises in Foveal Neural Circuits

RESEARCHERS HAVE KNOWN FOR almost a century that our fovea has a much lower sensitivity to rapidly changing visual inputs than our peripheral vision. This lesser sensitivity to rapid changes in visual stimuli is what enables humans to perceive continuous motion when we focus our central gaze on images in a flipbook, a movie, or a TV show.

Past work has shown that this perceptual difference might originate in the retina rather than in the higher brain centers. But the question has remained: Where in the retinal circuit does this originate, and what are the underlying neural mechanisms?

Intracellular recordings provide the clues. Scientists have now determined that cone photoreceptors in the fovea process incoming light in a different way from those in the peripheral retina—and that accounts for the difference in the temporal sensitivity of retinal signals sent to the brain. The discovery, based on recordings from individual neurons in the primate fovea, was reported by researchers at the University of Washington.¹

“We did the first intracellular recordings from cone photoreceptors and the retinal output neurons, the ganglion cells, and systematically compared the electrical responses in them with their counterparts in the peripheral retina. And what we found is that this difference in temporal sensitivity

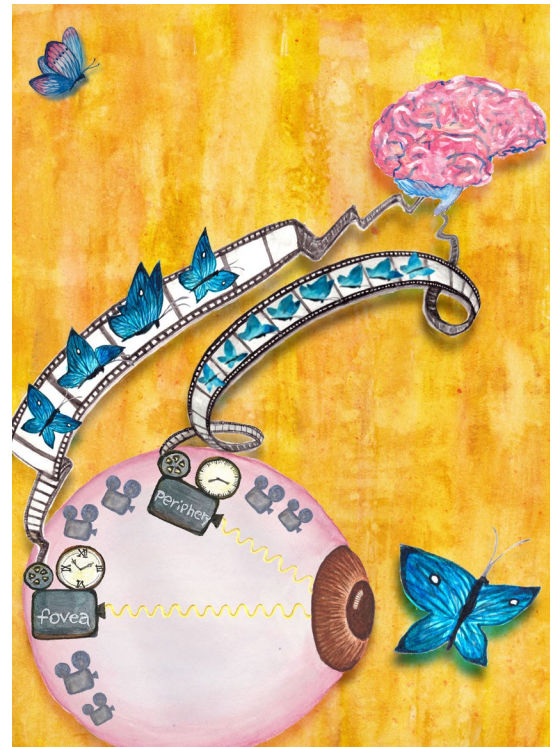
in our visual perception is present in the cone photoreceptors themselves,” said coauthor Raunak Sinha, PhD, a research fellow in the Department of Physiology and Biophysics at the University of Washington School of Medicine, in Seattle.

“We were further able to trace the reason down to the cellular mechanism,” Dr. Sinha said. “The phototransduction cascade—the very first stage of our visual processing—is essentially different between foveal and peripheral cone photoreceptors. That was a big surprise.”

Tracking the signals. These observations were made in vitro, using monkey retinas that continue to function normally for about 24 hours in the laboratory, Dr. Sinha said. The researchers were able to measure both the amount of light entering the individual photoreceptors and the output signals that they and cells downstream in the neural circuit emitted.

These measurements confirmed that peripheral cones transduce incoming light into electrical signals, which then flow sequentially to bipolar cells and retinal ganglion cells (RGCs) on their way to the visual cortex, he said. As they pass through the neural circuits to the brain, the signals are regulated at the synapses through the well-known mechanism of neural inhibition, he said.

But, in the fovea, molecular tests to detect inhibitory receptors on den-



SPEED OF PROCESSING. In this schematic illustration, visual information encoding the flight of a butterfly is conveyed by cone photoreceptors depicted as movie cameras with clocks that have different gradations. The “foveal camera clock” has coarser gradations, and the “film reel” carrying the information of the butterfly’s flight to the brain with the highest spatial resolution has a slower “frame rate,” with half as many frames compared with the peripheral film reel.

drites of ganglion cells showed that the dominant neural circuit—the midget ganglion cells—operates effectively independent of conventional synaptic inhibition. This is contrary to other RGCs, including peripheral midget ganglion cells, Dr. Sinha said.

This difference was a key insight for the researchers, but it does not account for differences in temporal sensitivity

between the 2 retinal regions, he said.

Instead, the electrical measurements showed that phototransduction in the cones exhibits a 2-fold difference in response time, which is nearly identical to the difference in perceptual sensitivity between foveal and peripheral vision. “Our results provide a simple explanation for a salient perceptual observation,” Dr. Sinha said.

How does this help? Going forward, the techniques used in the study will be important for researchers seeking to better understand diseases that perturb foveal signaling, such as macular degeneration, Dr. Sinha said. Furthermore, knowing that there is a fundamental difference in the computational strategies employed by foveal and peripheral retina will help shape the algorithms that scientists use to design visual prostheses to better mimic human vision, he said. —*Linda Roach*

1 Sinha R et al. *Cell*. 2017;168(3):413-426.

Relevant financial interests—Dr. Sinha: None.

LESSONS FROM TRAGEDY

Averting Stem Cell Tx Disasters

SEEKING TO PREVENT SEVERE VISION

loss associated with dry age-related macular degeneration (AMD), 3 women in their 70s and 80s underwent experimental autologous stem cell treatments at a Florida for-profit stem cell clinic in the summer of 2015. There they received bilateral intravitreal injections of adipose tissue-derived stem cells.¹

Devastating consequences. But instead of preventing vision loss, the procedures caused blinding complications in all 3 patients, including ocular hypertension, hemorrhage, lens dislocation, and retinal detachment. Within days of the procedure, they sought the help of ophthalmologists not connected with the stem cell clinic.

Before the experimental procedure, all 3 patients could drive. “The better-seeing eyes of the patients ranged from

20/30 to 20/50,” said Ajay E. Kuriyan, MD, at the University of Rochester Medical Center in Rochester, N.Y. “One year after treatment, visual acuity ranged from 20/200 to no light perception.”

Potential causes. “We suspect that cell preparation enzymes may have led to profound zonular weakness, experienced by all 3 patients,” said Dr. Kuriyan. In 1 patient, who was phakic at the time, the zonules had become so weak that her lenses moved forward, closing off the trabecular meshwork. The subsequent increase in intraocular pressure caused severe pain as well as vision loss.

“We took out both her lenses and cleared material that had been injected into the eye,” said Dr. Kuriyan. “She had a retinal detachment in one eye, which we reattached, but later developed a lot of scar tissue and the retina detached once again.”

All of the other patients’ eyes also developed severe retinal detachments and proliferative vitreoretinopathy. The authors hypothesize that the injected

GLAUCOMA GENETICS

Genes Point to 2 Key POAG Pathways

AN EXHAUSTIVE ANALYSIS OF THE “POAGome”—542 genes associated with primary open-angle glaucoma (POAG)—has identified inflammation and cellular senescence as the 2 most likely initiators of the molecular mechanisms that ultimately damage the optic nerve in the disease.

A “theory of everything”? Although the University of Pennsylvania researchers focused their conclusion on POAG, they also found hints that these 2 broad pathological processes might constitute the underpinnings of a long-sought “theory of everything”—explaining the pathology not only of POAG but also of other types of glaucoma.¹

“We used bioinformatics tools to look at glaucoma-related genes identified by published functional studies and genome-wide association studies, and this showed that most of these genes sing the same song,” said coauthor Venkata R.M. Chavali, PhD, assistant professor of ophthalmology at the Scheie Eye Institute in Philadelphia. “They funnel down into 2 important pathways that have never been reported to significantly influence POAG pathology.”

Inflammation and senescence pathways implicated.

The researchers reported that the largest subset of POAG-related genes activate the cytokines transforming growth factor alpha (TGF- α) and tumor necrosis factor beta (TNF- β), molecular growth factors linked to inflammation and senescence pathways. They also found possible involvement of genes related to a third senescence-related molecule, DNA transcription factor NF κ B, which if dysregulated can initiate a pathway leading to apoptosis.

Applying the findings. The results of the study are informing the genetic risk analyses that Scheie scientists are conducting in a 5-year, 7,000-patient study to examine glaucoma risk among African Americans, Dr. Chavali said. Among other goals, the project scientists hope to correlate genes, ancestral mix, and glaucoma risk in the POAG patients and controls, he said.

“In our area, we see so many African American patients who develop glaucoma 10 years younger than white patients and have 3 times the risk,” Dr. Chavali said. “Yet African Americans are underrepresented in the genetic databases on glaucoma.” —*Linda Roach*

1 Danford ID et al. *Prog Retin Eye Res*. Published online Feb. 20, 2017. doi:10.1016/j.preteyeres.2017.02.001.

Relevant financial disclosures—Dr. Chavali: None.

mesenchymal cells—known for their contractile property—stayed on the surface of the retina and contracted, leading to retinal detachment and scar tissue formation.

Time to educate patients. It's critical to inform patients about the risks of such stem cell clinics, said Dr. Kuriyan, who added that he was dismayed to discover the size of the stem cell clinic industry. It is difficult to confirm the number of these clinics, but 1 study found 187 unique websites offering stem cell procedures at 215 clinics in the United States alone. He and his colleagues hope to create a registry to collect information about similar emerging cases, some of which have surfaced following publication of their paper.

Clinicians can help, said Dr. Kuriyan, by alerting patients to red flags, by strongly suggesting patients steer clear of clinics that offer stem cell therapies alone, experimentally treat both eyes on the same day, or require patients to make out-of-pocket payments for a “clinical trial”—none of which are standard practices. Also, they can inform their patients that ClinicalTrials.gov is a registry, not a U.S. government endorsement of the study.

Issue of oversight. Parke et al. noted “these clinics have been operating largely without regulation because their stem-cell products have been self-identified as falling into a category not subject to regulatory oversight.”²

The FDA has released draft guidance statements, which make clear that autologous transplants should be under their jurisdiction and regulation, said Dr. Kuriyan. However, more guidance is on the way: The FDA is reportedly finalizing 4 new guidelines to clarify how stem cells may be used.³

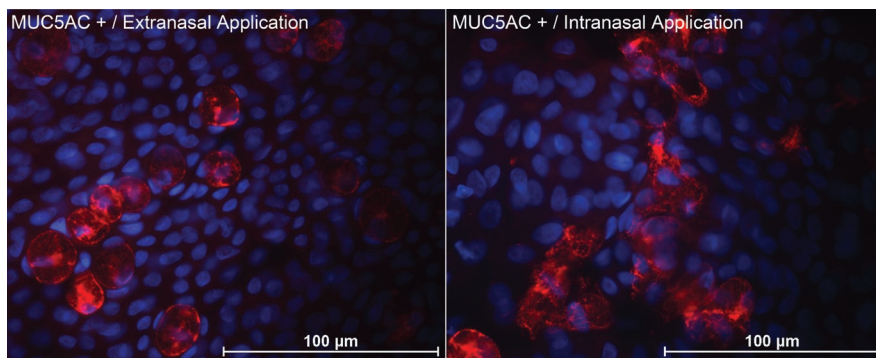
—Annie Stuart

1 Kuriyan AE et al. *N Engl J Med.* 2017;376(11):1047-1053.

2 Parke DW II et al. *Ophthalmology.* 2016;123(10):S62-S63.

3 aao.org/editors-choice/unapproved-stem-cell-treatment-blinds-3. March 17, 2017.

Relevant financial disclosures—Dr. Kuriyan: None.



INTRANASAL STIMULATION Novel Approach to Dry Eye

IN A SMALL RANDOMIZED CONTROLLED trial, production of aqueous tears and secretion of goblet cells increased following application of the Oculeve Intranasal Lacrimal Neurostimulator (Allergan).¹ This handheld device works by delivering electrical stimulation to the anterior ethmoidal branch of the trigeminal nerve in the nasal cavities. It potentially offers a new mechanism for treating dry eye disease—now largely managed with artificial tears and anti-inflammatory agents.

Methods and results. In the study, 10 patients with dry eye and 5 without underwent a screening visit and 2 treatment visits, randomized to either sham extranasal treatment or active intranasal treatment with the device. The researchers measured tear meniscus height using anterior segment optical coherence tomography. In addition, they applied an impression membrane to the surface of the conjunctiva to measure the ratio of degranulated to nondegranulated goblet cells as a marker of secretion. Measurements were taken before and after applications.

In patients with and without dry eye, treatment with the ILN significantly increased tear volume and effectively stimulated goblet cells, which produce stabilizing mucus in tears and are pivotal for maintaining tears' health and stability, said Stephen C. Pflugfelder, MD, from the Baylor College of Medicine in Houston. Results were better

SHAM OR ACTIVE TREATMENT. Mucin 5AC-stained impression cytology (x340). (Left) After sham application, all goblet cells appear to be in a non-degranulated form, with intact boundaries and mucous granules remaining in the cells. (Right) After active treatment, most of the goblet cells showed a degranulation pattern with disruption of cell morphology and release of mucous granules and mucin outside the cells.

when compared both with baseline measurements and with the results of the sham extranasal treatment.

Impact for patients. “These are encouraging results,” said Dr. Pflugfelder, “especially because this may make it possible to use patients' own neural pathways to stimulate tears without relying on a pharmacologic approach.” However, he added, there might be a nice synergy in using it with cyclosporine (Restasis) to increase the density of goblet cells, followed by Oculeve to stimulate their release.

Although this study did not evaluate symptom relief, a pilot study of 40 patients using the device 4 times daily reported a significant reduction in dry eye symptoms at each follow-up visit.²

Allergan has applied for FDA approval for the device, said Dr. Pflugfelder, and expects approval as soon as the third quarter of this year.

—Annie Stuart

1 Gumus K et al. *Am J Ophthalmol.* 2017;177:159-168.

2 Friedman NJ et al. *Clin Ophthalmol.* 2016;10:795-804.

Relevant financial disclosures—Dr. Pflugfelder: Allergan: C.