

## COMPREHENSIVE

# Sleep Disorders in Blind Patients: News From the Lab, for the Clinic

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In recent years, scientists working at the intersection of two historically well-developed fields, retinal physiology and circadian biology, upended the conventional view of retinal organization with the confirmation of a nonvisual ocular photoreceptor system.

The fact that the eye has functions beyond image perception holds the potential to explain why a significant proportion of patients with progressive degenerative ocular disease suffer from sleep disturbances. An understanding of these non-rod/non-cone photoreceptors might also explain seasonal affective disorder (SAD), jet lag and depression in the blind. It has the potential to influence intraocular lens selection for cataract patients. “The shocker is, you don’t need rods and cones to synchronize your circadian clock to the local light-dark cycle,” said Russell N. Van Gelder, MD, PhD. “There’s this whole other photoreceptive system lurking in the retina entraining your circadian system.” Dr. Van Gelder is professor and chairman of ophthalmology at the University of Washington in Seattle.

## The Eye Is a Camera, and Clock, Too

The notion of a parallel ocular universe began more than 80 years ago with the observation that blind mice continued to show pupil constriction in response to light.<sup>1</sup> Over time, researchers at about a dozen labs worldwide pursued the idea that the circadian and classical visual systems process

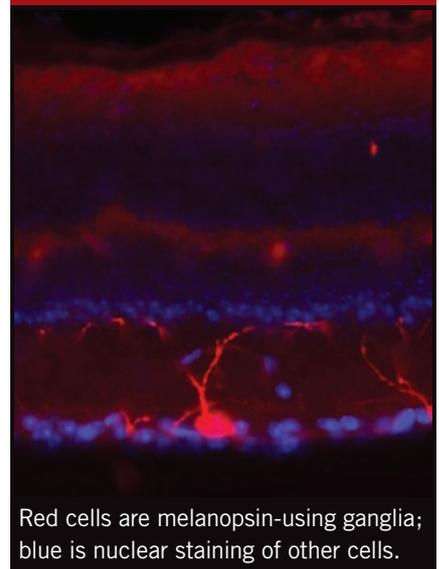
light information in different ways.

Russell G. Foster, BSc, PhD, chairman of both circadian neuroscience and ophthalmology at Oxford University, noted that by 2001, scientists had established the existence of a subset of photosensitive retinal ganglion cells (referred to in the literature as either pRGCs or ipRGCs, intrinsically photosensitive RGCs) that regulate a variety of different responses to environmental brightness, including sleep propensity.

This small subpopulation of RGCs responds directly to light and relays information along the nonvisual pathway to the brain’s circadian pacemaker, located in the suprachiasmatic nucleus of the hypothalamus, Dr. Foster said. They do this by employing the photopigment melanopsin, which is believed to set the circadian clock and initiate other nonimage forming visual functions. Dr. Foster has shown that loss of melanopsin in the pRGCs attenuates circadian responses to light.<sup>2</sup>

**Circadian drift.** “All of this suggests that diseases that kill melanopsin-using photosensitive retinal ganglion cells will result in behavioral changes that are manifested as sleep disorder problems or difficulty adjusting to changes in the light/dark cycle,” said Dr. Van Gelder. This research expands an understanding of the circadian clock, which governs the human habit of sleeping at night and waking in the morning. That clock, said Dr. Van Gelder, does not naturally have a 24-hour period. “It requires a daily

## Light, Yes, Pictures, No



Red cells are melanopsin-using ganglia; blue is nuclear staining of other cells.

light signal to stay synchronized to the outside world. Without that, the body’s clock will drift on its own.”

Consider, he said, two patients with ocular disease. John has ganglion cell disease and Jane has outer retinal disease. On January 1, both of their internal clocks tell them to awaken at 7 a.m. On January 2, Jane’s clock sees the sun rise and awakens at the same time. But John’s clock can’t see the light signal, so he wakes up closer to 7:30. On day three he wakes up around 8. By day 24, John’s inner clock awakens him a full half-day later, at 7 p.m., while Jane is still rising at 7 a.m.

**Counting sheep won’t help.** The discovery of photosensitive RGCs may explain why John’s sleep cycle is perturbed, while Jane remains on sched-

ule. “We suspect that sleep health and circadian health are probably dependent on the health of the optic nerves,” Dr. Van Gelder said. If the pRGCs are injured, it appears harder to keep the body’s clock synchronized. “They’re the only cells in the retina that encode brightness.”

If you were to place a mouse retina in a dish and expose it to light, from relatively dim to bright, the retina will respond linearly, functioning like a camera light meter, he explained. “This light meter controls at least three different aspects of physiology: circadian clock synchronization, pupillary light response and sleep. That is, it directly drives sleep and wakefulness in mice,” he said. “The obvious question is: What is the effect on human health if these cells are sick?”

**Studies link glaucoma and sleep problems.** One possible answer to that question comes out of a study conducted by Dr. Van Gelder himself, linking optic nerve disease to sleep disturbances.<sup>3</sup> His study, which monitored sleep patterns in a population of blind children, found that optic nerve disease is predictive of increased daytime napping in young visually impaired subjects. “We saw kids with end-stage glaucoma who had a hard time adjusting to the wake/sleep cycle of the outside world,” Dr. Van Gelder said. “If you’re blind from an optic nerve disease, you’re nine times more likely to have significant daytime sleepiness than if you are blind from other causes.”

A study by other researchers found that melanopsin-using cells in rats died after researchers induced an increase in IOP. “The results,” the researchers write, “suggest that serious attention should be paid to the function of the nonimage forming system in glaucoma patients in the future.”<sup>4</sup>

### How to Help Patients

Dr. Van Gelder advised ophthalmologists to be mindful of the potential interplay of certain ocular diseases and these novel RGCs. “We, as ophthalmologists, should expect that patients with advanced optic nerve disease may

## Implications and Applications

The discovery of novel photoreceptors within the eye is leading researchers down a number of new paths. Here are three areas they’ve been looking at.

**IOL SELECTION.** Cataract surgery has been associated with improvement in the sleep/wake cycle, possibly because the pRGCs are maximally sensitive in the “blue” (480 nm) part of the spectrum, while the yellow discoloration of a cataractous lens may reduce transmission of available photons to the retina. This has implications for what Dr. Foster called “the general global move toward implanting yellow, blue-filtering lenses.” The impact of blue-filtering lenses is a question worth pursuing, he said, noting that circadian rhythms might be affected if these lenses reduce the amount of blue light available to the melanopsin pigment.

**SEASONAL AFFECTIVE DISORDER.** Ignacio Provencio, PhD, a professor of biology at the University of Virginia, studies the genetics of circadian rhythms and has discovered that a mutation in a gene that codes for melanopsin may play a role in causing seasonal affective disorder (SAD).<sup>1</sup> This finding, said Dr. Van Gelder, could suggest that depression, common in the blind, may be a form of SAD. “Blindness,” he said, “may be like the effect of living in chronic winter.”

**NONVISUAL LIGHT PERCEPTION.** After ablating all rods and cones in mice, Dr. Foster and colleagues found that the mice were still fully able to constrict their pupils under bright light conditions.<sup>2</sup> “These findings raise some important clinical considerations regarding the diagnosis of ‘complete’ blindness,” Dr. Foster said. “Clearly, any such diagnosis should take into account both visual and nonvisual elements, that is, the health and function of both the rod and cone and pRGC photoreceptive systems.” Dr. Foster advised that blind individuals who are found to be light sensitive should expose their eyes to sufficient daytime light to maintain normal circadian entrainment and sleep/wake rhythms.

1 Roecklein, K. et al. *J Affect Disord* 2009;(114)279–285.

2 Foster, R. G. et al. *J Comp Physiol* 1999;169:211–220.

have difficulty synchronizing their lives with the light/dark cycle.”

**Ask some questions.** Therefore, he said, when physicians see patients who have a bilateral optic nerve disease, such as glaucoma, anterior ischemic optic neuropathy or optic atrophy, they should ask relevant questions: How’s your sleep? Do you feel in synch with day and night? Do you find yourself awake at inopportune hours and sleepy during others?

**Consider a referral.** Dr. Van Gelder advised referring patients who have trouble sleeping to a sleep disorder clinic. “This is a treatable disorder,” he said, citing the work of Alfred J. Lewy, MD, PhD, a psychiatrist at Oregon Health & Science University, who has been treating blind patients with melatonin for some 20 years.<sup>5</sup>

Though melatonin is available over the counter, Dr. Van Gelder cautioned ophthalmologists not to prescribe it without a referral to a sleep clinic be-

cause there are well-established treatment protocols. Melatonin will shift the clock, and shifting at the wrong time can actually make things worse, he said.

The point, said Dr. Van Gelder, is attending to those patients who suffer from sleep disorders. “We would never look at a patient with optic nerve hypoplasia without thinking they might have a systemic disease. But we don’t see a patient with end-stage optic nerve disease and immediately think that this person is at risk for sleep disorders. We should.”

1 Keeler, C. E. *Am J Physiol* 1927;81:107–112.

2 Foster, R. G. and M. W. Hankins. *Curr Biol* 2007;17:R746–R751.

3 Wee, R. and R. N. Van Gelder. *Ophthalmology* 2004;111(2):297–302.

4 Wang, H. Z. et al. *Chin Med J* 2008;121(11):1015–1019.

5 Lewy, A. J. *Cold Spring Harb Symp Quant Biol* 2007;72:623–636.