

# Neuro-endocrinology

# 20 BRIEFINGS

## SEEING THE LIGHT... IN A NEW WAY

### SUMMARY

Research over the past decade has shown that the rods and cones are not the only photoreceptors of the eye. There also exists a population of directly light-sensitive ganglion cells that act as brightness detectors and regulate a wide variety of different photosensory tasks, including the regulation of 24h circadian clocks, synthesis of the hormone melatonin, pupil size, and behaviour. These receptors may even help modulate our mood and sense of well-being.

*Figure 1. Calcium imaging of directly light sensitive ganglion cells in the isolated rd/rd cl mouse retina. The sequential images (1–11) show that illumination induced a significant increase in fluorescence of a calcium sensitive indicator loaded in the cells. In the last panel, the fluorescence intensity ( $\Delta F$ ) before, during, and after light stimulation (indicated by the bar) is plotted.*

Image prepared by Dr. Mark Hankins, Imperial College Faculty of Medicine.

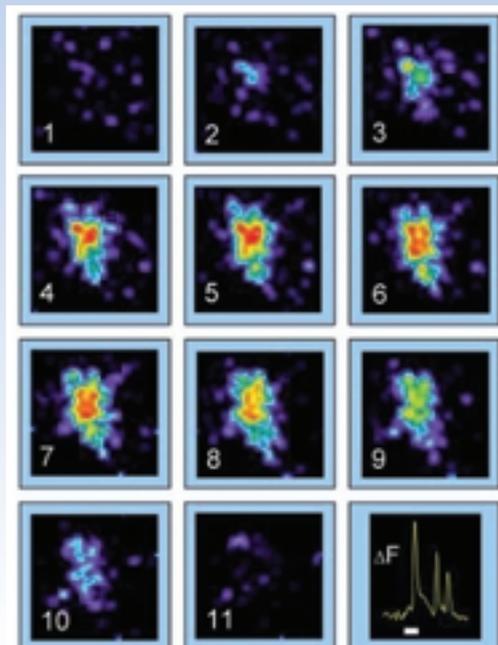
### A change of focus

Until recently, discussion that the eyes of humans and other mammals might contain a novel photoreceptor mechanism generated either bewilderment or hostile rebuttal by most eye researchers. It seemed impossible that something as important as another group of light-sensing cells could have been missed. The rationale was that the eye has been the subject of serious study from some 150 years, and in broad terms we understand how the eye functions. Photosensory rods and cones of the outer retina transduce light, and the cells of the inner retina provide the initial stages of signal processing before topographically mapped

signals travel down the optic nerve to specific sites in the brain for advanced visual processing. All responses to light were ascribed to this process. However, an interest in how circadian rhythms in body processes are regulated by light led to the discovery of an entirely new form of ocular light sensing that has little to do with image detection.

### Light, clocks, and novel receptors

Our circadian timing system “fine-tunes” physiology and behaviour to the varying demands of activity and rest and is synchronised (entrained) by the systematic daily change in the gross amount of light (irradiance) at dawn or dusk. The classic example of a mismatch between biological and environmental time is jet-lag. We ultimately recover from jet-lag primarily as a result of exposure to the light environment in the new time zone. Our circadian pacemaker or “master clock” resides in the suprachiasmatic nuclei (SCN) in the hypothalamic region of the brain (Figure 2). Destruction of this small paired nucleus abolishes 24 hour rhythmicity. Light information reaches the SCN through a dedicated pathway (the retinohypothalamic tract), which originates in the retina, and eye loss in every mammal, including humans, confirms that photoentrainment originates within



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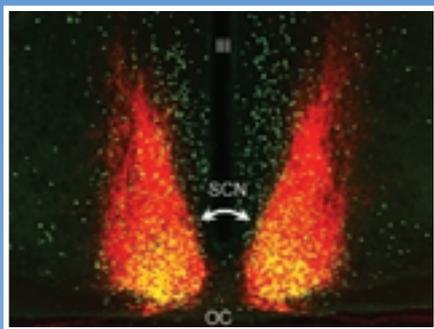


Figure 2. The paired SCN of a mouse shown in frontal section with neurons coloured in green and yellow and nerve fibres shown in red.

Photomicrograph prepared by Dr. Daniela Lupi, Imperial College Faculty of Medicine.

the eye. However, studies in mice and humans with hereditary retinal disorders during the 1990s produced some very puzzling results. Despite the fact that most of the rods and cones had been lost, and no conscious light perception was present, circadian entrainment to the light/dark cycle could still occur. It seemed extraordinary that the sensitivity of the circadian system to light did not parallel the loss of either rod or cone photoreceptors, or the loss of visual function. This work paved the way for the development of a transgenic mouse model (*rd/rd cl*) which lacks all functional rods and cones. Despite the ablation of the classical photoreceptors, both circadian entrainment and the regulation of pineal melatonin production remained intact in these animals. There had to be another light sensing mechanism within the eye! Furthermore, studies on *rd/rd cl* mice showed that a number of other physiological and behavioural responses to environmental brightness are either intact or retained at some level in the absence of the rods and cones (e.g. pupil constriction). This suggests that novel photoreceptors might contribute to very many

more aspects of mammalian physiology and behaviour than previously suspected. For example, light level modulates sleep, cortisol secretion, heart rate, and alertness, performance and mood. Could these irradiance responses also be influenced by non-rod, non-cone ocular photoreceptors? Work currently underway suggests that this is very likely.

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*“...individuals will be circadian-blind with disrupted rhythms...”*

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### Seeing the blues

The cellular localisation of the non-rod, non-cone ocular photoreceptors has been based upon a number of different lines of evidence. The most convincing approach employed the isolated *rd/rd cl* mouse retina in combination with techniques to image levels of calcium ions in neurons. Approximately 1% of the neurons in the retinal ganglion cell layer responded to light directly (Figure 1). Detailed analysis showed that there exists a heterogeneous coupled network of intrinsically photosensitive neurons in the ganglion cell layer of the mouse retina that detects environmental brightness. These photoreceptors employ a previously uncharacterised, opsin/vitamin A-based photopigment with peak sensitivity in the blue part of the spectrum near 480 nm. Furthermore, behavioural studies in humans suggest that we also possess an equivalent of this mouse photopigment, although the gene encoding it still awaits unambiguous identification.

### Future vision

The eye has been considered the best characterized part of the central nervous system, and the fundamental questions about the eye were considered answered. The discovery of a new light detecting system tells us that we still have a lot to learn about the eye. Much of this information will have important clinical implications; not least on the classification of blindness. The loss of rod and/or cone photoreceptors does not necessarily mean that individuals will be “circadian-blind”. In addition, it seems likely that there will be conditions where the novel photoreceptor system has been lost, and individuals will be circadian-blind with disrupted rhythms, but still possess a working image-detection system. Ophthalmologists are just beginning to appreciate the full consequences of eye loss. A state that shatters an individual’s sense of both space, and time.

#### Author:

Russell G. Foster  
Department of Visual Neuroscience  
Imperial College Faculty of  
Medicine  
London, UK

#### Editor:

Dr R John Bicknell  
Laboratory of Neuroendocrinology  
The Babraham Institute  
Cambridge CB2 4AT UK  
john.bicknell@bbsrc.ac.uk

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