Furthermore, excitotoxic insults, like other insults, can induce neurons to undergo cellular suicide (programmed cell death), and intermediate increases in intracellular Ca^{2+} concentrations can stave off this death programme[9,10]. Although NCX has low affinity for Ca^{2+}, its inhibition can prolong the transient large fluctuations in Ca^{2+} that are evoked by the depolarization of sympathetic neurons[11]. So, one could envisage a situation in which an initial harmful burst of Ca^{2+} influx is followed by relative normalization of Ca^{2+} levels, and calpain-induced NCX cleavage helps to elevate these late Ca^{2+} levels to the point at which programmed cell death is inhibited.

As Bano *et al.*[1] point out, calpain-induced NCX cleavage has an intriguing parallel in the caspase-induced cleavage of another Ca^{2+}-extrusion pump, PMCA[12]. Perhaps both of these cleavage events can either promote or inhibit cell death in different circumstances, specifically acting at low injury levels to ensure that a commitment to undergo programmed cell death does not occur casually. ■

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Neurobiology

Bright blue times

Russell G. Foster

The discovery of light-sensitive neurons that can adjust our body clocks prompted a search for their light-detecting molecule. We now know the identity of this pigment — and that these cells do more than was thought.

Our in-built ability to tune our body clocks to day and night relies on a special set of light-sensitive neurons in the eye. Three new papers — two in this issue[1,2] and one in *Science*[3] — provide strong evidence that melanopsin is the pigment that allows these cells to respond to light. Yet another paper in this issue[4] provides the first detailed description of the cells in a primate.

Until a decade or so ago, we thought we understood the workings of the vertebrate eye. The rods and cones (photoreceptors) of the outer retina detect light, with cells of the inner retina providing the initial stages of visual processing, before ganglion cells convey information to the brain via the optic nerves (Fig. 1a). But evidence for another light-sensing system in the eye — separate from the rods and cones — began to accumulate in the 1990s. This came from researchers, studying the body clock (circadian rhythms), who appreciated that the eye performs two quite different sensory tasks. Its familiar function is to collect and process light to generate an image of the world. But it also provides a measurement of environmental brightness at dawn and dusk, to align circadian time to environmental time.

Circadian biologists had a problem locating this function within the known structures of the eye, and, in an attempt to find the cells responsible, they used mouse models that lacked rods, cones or both. Remarkably, the loss of all types of known photoreceptor had little effect on the animals' ability to tune their circadian system to light[5,6], but loss of the eyes abolished this ability completely. So there had to be another light sensor in the eye. Subsequently, these sensors were shown to contribute, together with the rods and cones, to the regulation of pupil constriction and of other responses to light[7]. Because these photoreceptors are associated with brightness detection, the collective term 'non-image-forming photoreceptor system' has been used to describe them; the 'image-forming' system refers to the rods and cones.

Several groups then began to investigate which neurons mediate non-image-forming responses to light — and what makes them light-sensitive. The answer to the first problem was provided by the discovery that a small subset (around 1%) of retinal ganglion cells respond to light directly[8,9], in part through an increase in intracellular calcium concentrations[9] (Fig. 1b). Finding what makes these cells responsive to light has been more difficult.

The known photopigments found in animals combine an opsin protein with a vitamin-A-based light-absorbing molecule (chromophore) called 11-*cis*-retinaldehyde. The first stage of light detection involves the absorption of a photon by 11-*cis*-retinaldehyde, and the photoisomerization of this molecule to the all-*trans* state (Fig. 2). This allows the opsin to trigger a phototransduction cascade that ultimately changes the cell's electrical activity. All opsin–vitamin-A photopigments have a characteristic absorption profile, which allows them to be identified on the basis of their spectral responses to light. The photopigment in the mouse non-image-forming photoreceptors has a maximum sensitivity in the blue part of the spectrum, at a wavelength (λ_{max}) of 479 nm (ref. 7). This photopigment was originally termed opsin photopigment 479 (OP^{479}), but its molecular identity remained a mystery.

Melanopsin[10] (also called Opn4) soon emerged as the best candidate. It is expressed in the photosensitive ganglion cells[8,9], and its genetic ablation attenuates circadian and pupil responses to light. Furthermore, removing melanopsin in mice lacking all functional rods and cones abolishes such responses completely[11]. Yet although these studies showed that melanopsin is essential for photosensitive ganglion cells to respond to light, they could not explain how melanopsin works.

Melyan *et al.*[1], Qiu *et al.*[2] and Panda *et al.*[3] have now assessed the function of melanopsin by combining its expression with physiological assays of cellular photosensitivity. All three papers show that melanopsin can confer photosensitivity on non-photosensitive cell types, and that specific forms of retinaldehyde (especially 11-*cis*-retinaldehyde) are required. In short, they show that melanopsin acts as a photopigment.

Beyond this remarkable finding, the papers differ in some of their conclusions. Qiu *et al.*[2] and Panda *et al.*[3] show that melanopsin has a λ_{max} very close to 480 nm — so OP^{479} seems to be melanopsin. However, Melyan *et al.*[1] (and previously Newman *et al.*[12]) suggest that melanopsin has a λ_{max} closer to 420–430 nm. There is no obvious explanation for this difference, but it might relate to the immediate environment of the expressed photopigment. For example, pH conditions combined with differences between mouse[2,3] and human[1] melanopsin might be responsible.

Melyan *et al.* and Panda *et al.* also provide evidence that melanopsin exhibits bistability — the ability to bind alternately to 11-*cis*- and all-*trans*-retinaldehyde, and to act as both a sensory pigment and an isomerase for photopigment regeneration (Fig. 2). But Qiu *et al.* suggest otherwise. This discrepancy might reflect the different cell types used; for example, Qiu *et al.* expressed melanopsin in cells that show endogenous retinoid metabolism.

All three groups also look at the melanopsin-evoked phototransduction cascade. There is broad consensus from these and previous[9] studies that light will ultimately trigger the release of calcium ions inside the ganglion cells, and that this involves some kind of interaction of melanopsin with a G protein (a member of a diverse family of proteins that link receptors to signalling cascades). Although our knowledge is far from complete, this phototransduction

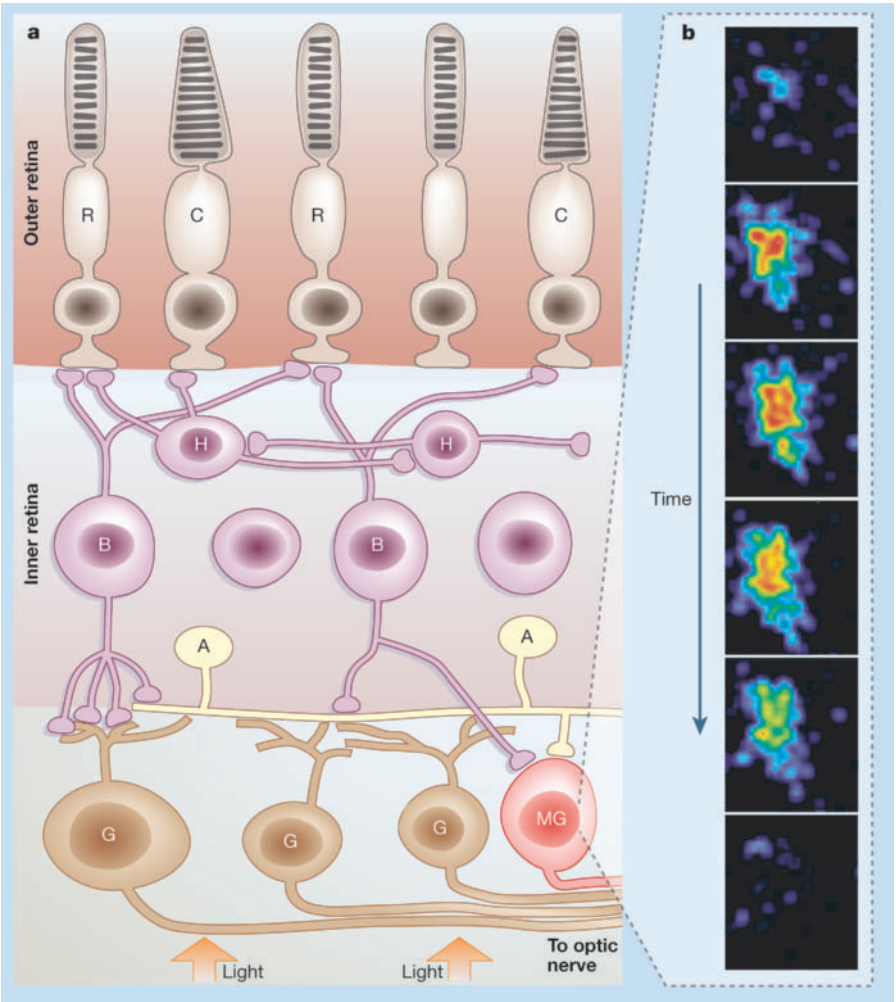

Figure 1 **The basic cell types of the vertebrate retina.** a, **The rods (R) and cones (C) convey visual information to the ganglion cells (G) through the bipolar cells (B). Horizontal cells (H) allow lateral connections between rods and cones. Amacrine cells (A) allow lateral connections between bipolar and ganglion cells. The optic nerve is formed from the axons of all the ganglion cells. A subset of ganglion cells (MG cells) also detects light directly; for this, they require the photopigment melanopsin, as now confirmed[1–3].** b, **Light, via melanopsin, causes changes in Ca^{2+} levels in MG cells[9] (a fluorescent Ca^{2+} indicator was used here). Counterintuitively, light passes through the transparent ganglion layer to reach the rods and cones.**

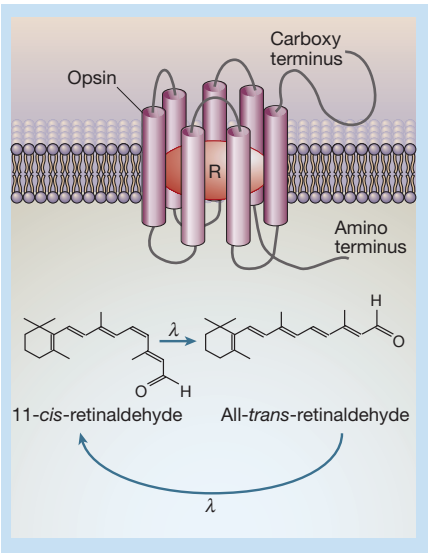

Figure 2 **Animal photopigments consist of an opsin protein coupled to the 11-*cis* form of retinaldehyde (R). In response to light of an appropriate wavelength (λ), 11-*cis*-retinaldehyde absorbs a photon and is photoisomerized to all-*trans*-retinaldehyde. This changes the opsin's conformation, initiating a phototransduction cascade that includes Ca^{2+} changes in light-sensitive ganglion cells. Some invertebrate opsins, and possibly melanopsin, can act as both a photosensor and a photoisomerase — driving all-*trans*-retinaldehyde back to the 11-*cis* configuration.**

cascade seems very different from that of rods and cones. In fact, it is more like that of an invertebrate photoreceptor, raising interesting questions about the evolution of ganglion-cell photosensitivity.

And what of the fourth new paper[4]? Behavioural studies in humans indicate that we possess a non-image-forming photoreceptor system like that of rodents. Dacey *et al.*[4] have now examined the photosensitivity of melanopsin-expressing ganglion cells in macaques — a monkey with a very similar visual system to ours. The authors find that, in general terms, the responses of these cells are like those of rodents, again showing a spectral response with a λ_{max} near 480 nm. This begs the question of why blue light is so important. We can only guess at the answer, but perhaps it is no coincidence that 480-nm light dominates the wavelengths at dawn and dusk. Could it be that the main role of these ganglion cells is to detect twilight?

Previous studies in rodents have also shown that the image-forming and non-image-forming systems interact[8,11]; Dacey *et al.* extend our understanding of these interactions. Perhaps their most fascinating finding is that the short-wavelength-detecting cones attenuate the light responses of melanopsin-expressing ganglion cells, whereas the rods and medium- and long-wavelength cones provide an excitatory input. Again, an ecological explanation remains unclear. Dacey *et al.* also show that these ganglion cells project to the lateral geniculate nuclei — the brain structure that relays image-forming information to the visual cortex. This observation, along with other recent work[13], supports the idea that the non-image-forming system contributes to aspects of visual perception.

This final observation completes a circle of thought. Originally, rods and cones were assumed to be the only photoreceptors of the eye. Then it was discovered that the loss of rods and cones had little effect on circadian responses to light, suggesting that the eyes use different photoreceptor systems for these different sensory tasks. Next, pupil constriction and circadian responses to light were shown to arise from an interaction between the two receptor systems. Finally, it now seems likely that photosensitive ganglion cells impinge directly upon image formation. Clearly, all future experiments on human light detection will have to consider the relative contributions of both photoreceptor systems. ■

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