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Photopigments and circadian systems of vertebrates

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Abstract

In the retinal degeneration (rd) mouse the absence of rod cells and the progressive loss of cones does not result in a decrease in circadian phase shifting responses to light. By contrast, rd/rd mice are unable to perform simple visual tasks. In addition, rodless transgenic mice, and mice homozygous for the retinal degeneration slow (rds) mutation, show unattenuated circadian responses to light. Collectively these data suggest that cone cells lacking outer segments are sufficient to maintain normal circadian responses to light, or some unidentified photoreceptor within the retina. An action spectrum for circadian responses to light in rd/rd mice, and molecular analysis of retinally degenerate mice and blind mole rat eyes, suggests the involvement of a mid-to-long wavelength sensitive cone opsin in photoentrainment. Extraocular photoreceptors of non-mammalian vertebrates are currently being analyzed in order to identify functional and evolutionary similarities between visual and non-visual photoreceptor systems.

Keywords: Circadian photoreception; CSF-contacting neurons; Extraretinal photoreception; Opsin; Retinal degeneration

1. Introduction

Daily or circadian rhythms are driven by endogenous pacemakers that have periods close to, but rarely exactly, 24 hours. In order to function adaptively, circadian systems must be synchronized (entrained) with the astronomical day, and for the majority of circadian rhythms internal time is entrained by the irradiance changes at dawn and dusk. While it is clear that photoreceptive mechanisms are used to regulate the clock, our understanding of these sensory systems remains superficial. Frequently the nature of the photopigment and even the location of the photoreceptor cells remain unknown.

In the vertebrates, all photoreceptors appear to arise from the diencephalon, and are found within the retina, pineal complex (pineal, parapineal, parietal, frontal organ) and 'deep brain' [1]. Despite this common origin, these photoreceptors differ markedly and have been broadly grouped into two classes: visual or retinal photoreceptors which mediate image detection, and extraretinal photoreceptors which detect irradiance changes and regulate circadian and other autonomic physiological responses to light. In

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mammals this distinction is blurred. Mammals lack extraretinal photoreceptors, but have unidentified photoreceptors within the eye that regulate circadian responses to light [2].

2. Circadian photoreception in mammals

We have previously shown that circadian responses to light are unaffected in mice homozygous for the *retinal degeneration* mutation (rd/rd) [2]. This mutation results in the rapid loss of rods followed by the more protracted loss of cones [3,4]. The remaining cone cells appear to lack outer segments. Despite this tremendous loss in visual machinery, the site of circadian photoreception still resides within the degenerate eye because bilateral enucleation of rd/rd animals abolishes all circadian responses to light. These data suggest that circadian photoreception is either normally performed by small numbers of cone photoreceptors (which lack outer segments), or alternatively, there may exist an unrecognized class of photoreceptive cell in the mammalian retina that is unaffected by the rd mutation and that functions normally to regulate rhythmic physiology and behavior [2]. In this paper we will review our more recent findings and address these alternatives.

2.1. Circadian and visual responses in aged retinally degenerate mice

The progression of photoreceptor degeneration in rd/rd mice commences early in post-natal development with the loss of rods, followed by a more protracted loss of cones. Our original studies examined circadian responses to light in rd/rd and normal mice 80 days of age, and we found that phase shifting responses were identical. If the surviving cone cell bodies mediate circadian responses to light, and assuming that the circadian system uses some photon counting mechanism (Section 2.5), then we would expect the photosensitivity of the circadian system to decline with age and parallel the loss of cones in the rd/rd retina. We have examined circadian photosensitivity in aged rd/rd and normal mice (80–800 days of age) and find no attenuation of response. Thus, there appears to be no correlation between circadian responses to light and rod or cone cell loss in the rd/rd retina [5,6].

In parallel with our analysis of circadian responses to light, we have developed behavioral assays to assess the visual capabilities of retinally degenerate mice. A mouse is placed in a two-chambered cage with an escape window placed in the center of the dividing wall through which the mouse can move freely. The mouse can be given a mild electrical shock (0.25 mA) through the wire floor of either side of the cage, but never both chambers at the same time, allowing the animal to escape to the neutral chamber when the shock is applied. For the first two days of testing, the mouse is tested in dim red light and given a 10 second shock every 60 seconds for 20 trials. The mouse learns to escape the shock only by jumping through the window to the neutral side of the cage. For the following 14 days, a 5 second white light pulse (25 $\mu W/cm^2$) is administered prior to the electrical shock. Escape to the neutral chamber and hence avoidance of the shock demonstrates visual competence. Normal mice successfully learn to avoid the shock, but rd/rd mice seem incapable of learning this task. However, the substitution of a 3 kHz tone for the light pulse resulted in classical conditioning of both normal and rd/rd animals [5]. Recall that light-induced circadian responses of rd/rd mice remain unattenuated, yet these animals fail to respond to this simple visual task. These data illustrate major differences between visual and circadian light detection.

2.2. Rod photoreceptors are not required for circadian responses to light

Circadian responses to light were investigated in transgenic mice carrying an integrated fusion gene consisting of a 1 kb fragment of the human rhodopsin promoter linked to the attenuated diphtheria toxin (DT-A) gene. Morphological analysis of the retinae demonstrates that rod photoreceptors are eliminated, but cone cell bodies (with no outer segments) remain for at least 11 weeks after birth [7]. Despite this loss, circadian locomotor rhythms entrain to a light : dark cycle, and free-running rhythms in constant darkness can be phase shifted by light and responses may be even larger in the absence of rods (Fig. 1) [8]. A complete irradiance response analysis for these rodless transgenic animals is currently underway. These preliminary data support our results in rd/rd mice

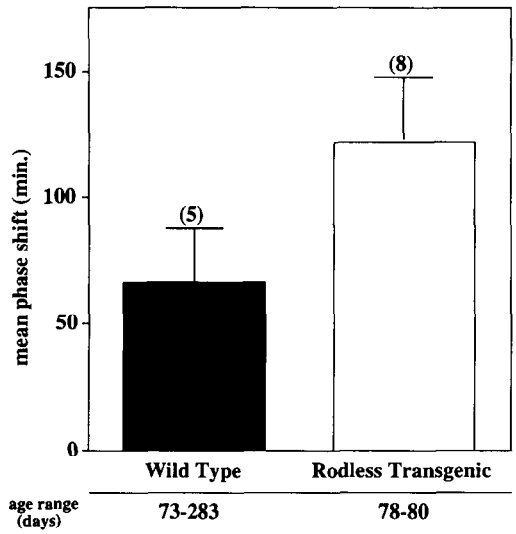

Fig. 1. Histogram representing mean phase shifting responses of C57BL wild-type and rodless transgenic mice of various ages. Transgenic mice carry a DT-A gene under the control of the human rod opsin promoter. Phase shifting paradigm is identical to description in legend for Fig. 2. Sample sizes are indicated in parenthesis. Error bars represent the standard error of the mean.

and demonstrate that rod photoreceptors are not required for circadian responses to light. However, these data cannot entirely exclude rod photoreceptors from playing a role in circadian photoregulation.

2.3. Photoreceptor outer segments are not required for circadian responses to light

Another retinal mutation, rds (*retinal degeneration slow*), in the C3H mouse strain has provided an additional approach to the question of which elements in the eye mediate circadian responses to light. In rds/rds mice, rod and cone photoreceptors fail to develop outer segments and as a result both classes of photoreceptors gradually degenerate over the course of a year [9,10] (rd/rd mice photoreceptors develop outer segments but these are lost as retinal degeneration proceeds). In rds/rds mice approximately half of all photoreceptor cell bodies have degenerated by three months, and virtually all are gone by one year of age. Our studies have shown that circadian responses to light are identical in rds/rds, rd/rd and +/+ genotypes (Fig. 2), even in aged animals [5,6]. In addition to supporting our conviction that only a small population of photoreceptor cells are required for the circadian system to entrain, these data also provide overwhelming evidence that photoreceptor cell outer segments are not required to elicit a circadian response to light.

2.4. Spectral sensitivity of circadian responses to light resemble mid-to-long wavelength sensitive cones

We have now completed an action spectrum for phase-shifting circadian rhythms in rd/rd and +/+ mice. From a series of irradiance response curves at six different wavelengths, we derived an action spectrum that closely fits a visual pigment nomogram with a wavelength of maximum sensitivity near 505 nm (Provencio and Foster, in preparation). Because rods are not required for circadian responses to light (Sections 2.1 and 2.2) then cones become obvious candidates for circadian photoreception. To date, there is evidence for two types of cones within the mouse retina. Electroretinogram (ERG) and behavioral studies have shown two sensitivity maxima, a green-sensitive cone near 510 nm and an ultraviolet sensitive cone near 370 nm [11]. The similarity of our action spectrum results (505 nm) to the spectral sensitivity of the green cones (510 nm) suggests that the green cones, or a mid-to-long wavelength sensitive cone opsin, may mediate photoentrainment in mice.

2.5. Molecular analysis of the remaining opsins within the rd eye

To date, only three opsins have been cloned from the mouse retina (M. Applebury, personal communication). On the basis of their similarity to human opsins and ERG responses recorded from the mouse eye they can be classified as: rod opsin, UV/blue cone opsin, and red/green cone opsin. In an attempt to implicate these opsins in circadian responses to light, we initially performed Northern blot analysis to quantify the loss of these opsins from the degenerating (rd/rd) mouse retina. Rod opsin mRNA disappeared by four weeks of age, followed by the gradual loss of UV/blue and red/green cone opsins to below detectable levels by 45 weeks of age [6]. These data suggest two broad alternatives: either one

or more of the known opsins mediates circadian responses to light and occurs at extremely low levels in the degenerate retina, or none of the known opsins mediate circadian responses to light, and there is a unique 'circadian' opsin in the retina.

To achieve greater sensitivity we have extended our molecular characterization by using RT–PCR (reverse transcriptase–polymerase chain reaction). We have succeeded in amplifying both the red/green cone and UV/blue cone opsin, but failed to identify any rod opsin mRNA in the rd/rd retina over one year of age. As the two cone opsin messages remain, both proteins could play a role in mediating circadian responses to light. Our action spectrum results suggest the involvement of the red/green cone opsin (Section 2.4), but as the action spectrum did not explore the effects of wavelengths in the UV range, we cannot dismiss the involvement of an UV opsin in photoentrainment.

Arguments for the involvement of red/green cones in circadian regulation would be strengthened if we could show that these cells are connected to the suprachiasmatic nuclei, the primary site of the mammalian circadian pacemaker. We are currently using the Bartha strain of porcine pseudorabies virus (generously donated by J.P. Card, University of Pittsburgh) for tract tracing studies on the mouse retinohypothalamic tract. The infective properties of this virus are 'circadian system-specific' [12]. When injected into the eye of an rd/rd or normal mouse the virus labels the suprachiasmatic nuclei (SCN), but the initial wave of the infection leaves visual projections uninfected [13]. This technique offers us the possibility of tracing the connections between defined retinal cells and clock centers within the brain (SCN).

It is worth stressing that although the red/green cone opsins and photoreceptor cell bodies remain in the rd/rd retina, most of the red/green cones degenerate. If these mid-to-long wavelength sensitive cones (lacking outer segments) mediate circadian responses to light, then one must explain the observation that circadian responses to light remain unattenuated in aged rd/rd mice. We recently proposed a model that could account for loss of photoreceptors with no loss in sensitivity [14]. This model can be summarized as follows: if circadian photosensitivity were directly related to photoreceptor number (i.e. photons are counted by an additive process), then one would expect to observe a decline in circadian responses to

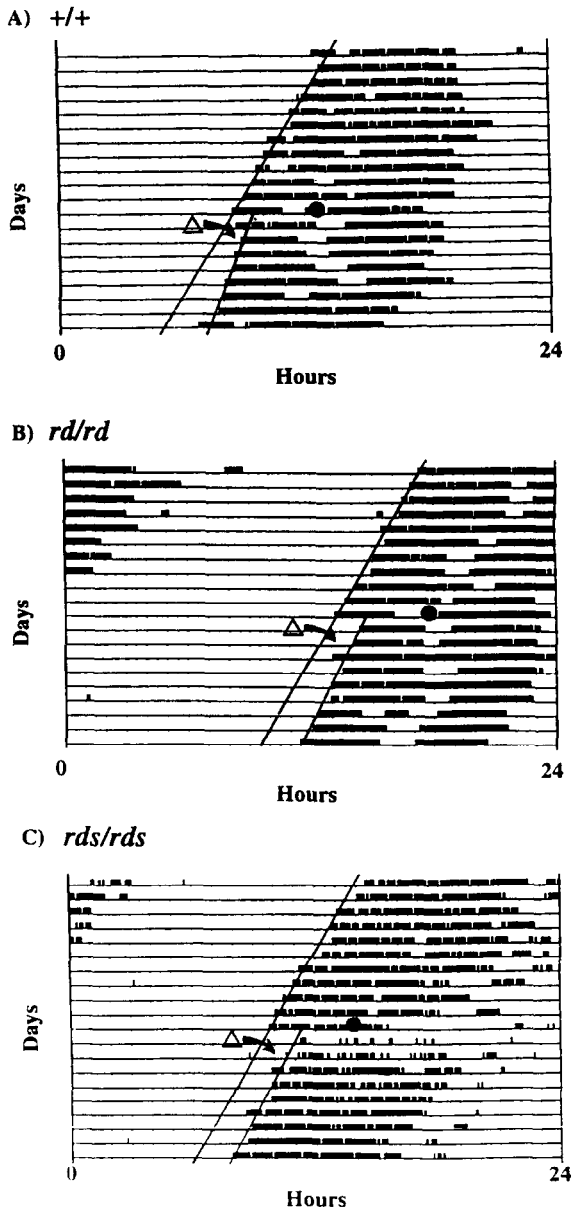

Fig. 2. Representative free-running locomotor activity rhythms of C3H +/+ (A, $n = 48$), rd/rd (B, $n = 54$) and rds/rds (C, $n = 45$) mice housed in complete darkness in cages equipped with running wheels. Each record is plotted on a 24 hour scale with subsequent days plotted from top to bottom. Black bars represent bouts of concentrated wheel-running activity. After 10–12 days in constant darkness, the mice were individually placed into a light pulse apparatus and exposed to a 15 minute pulse of monochromatic light (515 nm; 1×10^{-1} $\mu W/cm^2$) at circadian time 16 (CT16), four hours after activity onset (CT12). The time of the pulse is represented by a filled circle. After an additional 10 days in darkness, the magnitude of the phase shift was measured as the difference between the steady state phase of the free-running rhythm before and after the pulse (Δ).

light as photoreceptors disappeared from the retina. If, however, the output from circadian photoreceptors is averaged, then a progressive loss of circadian sensitivity would not be observed until the number of photoreceptor cells approached zero. Such a system would require relatively few photoreceptive cells to show normal responses to light. In this case the sensitivity-limiting step is 'down stream' from the photoreceptors and the system would be buffered from the degenerative loss of photoreceptive elements.

2.6. Analysis of a blind subterranean mammal: the blind mole rat (Spalax ehrenberghi)

The blind mole rat, *Spalax ehrenberghi*, is a subterranean mammal whose visual system is naturally drastically reduced. These animals have minute subcutaneous eyes that lack a functional lens. As a result, the eye lacks any image forming capability [15]. In addition, projections to visual centers of the brain are reduced by 87–93% when compared with other rodents. By contrast, the relative size and

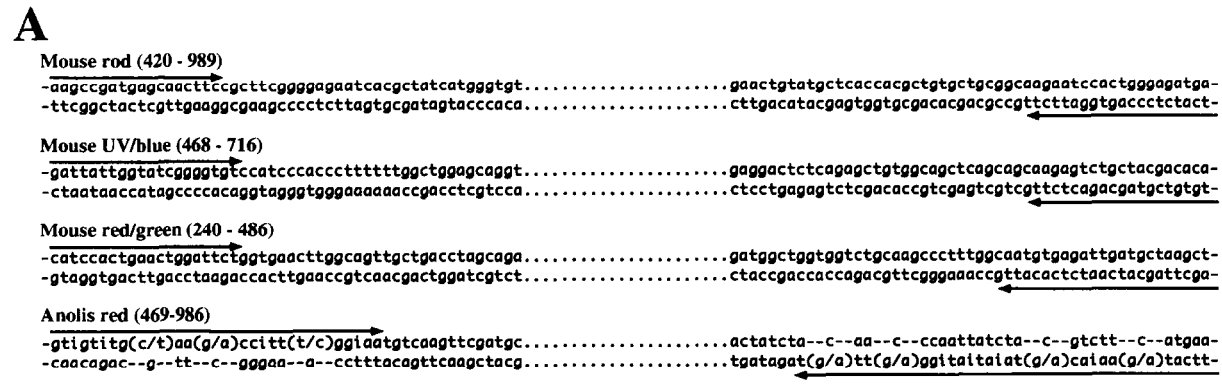

Fig. 3. (A) Primer sequences used for RT–PCR analysis of the mole rat eye. Primers were designed against conserved regions of the published mouse rod [33] and UV/blue cone [34] opsin sequences and the red/green cone opsin sequence donated by M. Applebury (personal communication). The universal cone primer was designed against regions of the *Anolis* red cone opsin protein [35] that are highly homologous between several different species. Arrows span the primer sequences used. Numbers in parentheses denote the bases of the coding region that are bounded by the primers (position 1 corresponds to the first base of the methionine start codon). (B) Partial amino acid sequence of the *Spalax* clone and other known long-wavelength sensitive cone opsins. The clone spans the region between Helix II and Helix III of the opsin molecule. Sequences with 100% identity between species are boxed. Mouse opsin sequence (a) has been determined by M. Applebury (personal communication). Other red/green sequences (b–f) have previously been reported by Nathans et al. [36], Kojima et al. [37], Kuwata et al. [38], Kawamura and Yokoyama [35], and Johnson et al. [39], respectively.

morphology of the suprachiasmatic nuclei (SCN), in which the circadian pacemaker resides, is identical between *Spalax* and other rodents. Moreover, the retinal projections to the SCN in the mole rat are increased twenty-fold [16]. We have recently shown, using viral tract tracing techniques, that all the ganglion cells within the retina project to the SCN (Cooper and Provencio, unpublished data). Although visual responses are lacking in *Spalax*, photic entrainment of locomotor and thermoregulatory activity rhythms persist (see Ref. [15]). With these characteristics, these eyes have been considered to be 'pure' circadian photoreceptors.

Immunohistochemical evidence suggests the existence of a rhodopsin-like protein in the mole rat eye [15]. Additional evidence for a rod-like pigment comes from immunoblot and genomic DNA analysis of the mole rat [17]. Using primers for the three mouse opsins (rod, UV/blue cone and red/green cone) and a pair of degenerate universal cone primers, we conducted RT–PCR on RNA isolated from blind mole rat eyes in an attempt to PCR-clone any opsins present in the eye. Only the mouse red/green primers produced an amplification product. This cDNA shows high sequence homology to both the mouse and human green cone opsins (Fig. 3). Although these preliminary data do not exclude the possibility that a rod and/or blue cone opsin exist within the mole rat retina, they would support our proposal that a mid-to-long wavelength sensitive cone opsin plays a major role in the regulation of mammalian circadian responses to light.

3. Circadian photoreception in non-mammals

The knowledge that non-mammalian vertebrates possess anatomically and functionally distinct classes of photoreceptors has not resulted in an equal exploration of these sensory systems. We know very little about 'extraretinal' or 'encephalic' photoreceptors, and this paucity of information is certainly related to their accessibility, and hence ease of experimental manipulation. The relative ease of retinal neurobiology has dominated photosensory physiology to such an extent that the role of extraretinal photoreceptors in physiology and behavior is often ignored.

The demonstration of extraretinal photoreceptors has been based almost exclusively upon ablation or localized illumination of putative photoreceptors. For example, the first demonstration of extraretinal and extrapineal photoreceptors was in 1911 by Carl von Frisch, who blinded and pinealectomized European minnows (*Phoxinus phoxinus*) and showed that animals would still show color changes in response to illumination of the head [18]. Subsequently, von Frisch found that lesions within the diencephalon would completely block this response to light, and concluded that there must be photoreceptive elements within the diencephalon. This approach was used by others in the 1930's to show that ammocoete larvae have a basal brain photoreceptor, and from the 1930's–1970's to show that birds regulate circadian and gonadal responses to photoperiod by brain photoreceptors (e.g. [19]). More recent studies made use of chronically implanted fiber optics or small, low irradiance, radioluminous beads implanted into the brain of birds to trigger gonadal induction or circadian entrainment when located within the hypothalamus or lateral septal areas (e.g. [20,21]).

While the majority of studies on the deep brain photoreceptors have been on birds, significant results have also been obtained in the other groups of vertebrates. For example, extraretinal photoreception was examined in four families (eight species) of lizard, including the green anole (*Anolis carolinensis*). In all species, blinding and removal of the pineal complex (pineal and parietal organ) did not prevent animals from entraining circadian locomotor rhythms to a light : dark cycle. The conclusion was that photoreceptors within the brain can fully mediate circadian entrainment in lizards [22].

3.1. Cerebrospinal fluid (CSF)-contacting neurons

While it has been possible to demonstrate that particular areas of the nervous system are photosensitive by surgical removal and directed illumination, the identification of the photoreceptive cells within these tissues has proved more difficult. Most recently, the characterization of circadian photoreceptors has attempted to identify opsin and chromophore within the cells and tissues suspected of circadian photoreception.

Action spectrum techniques were particularly helpful in the initial characterization of pineal and

deep brain photoreceptors. In the isolated chick pineal, an action spectrum for suppression of the activity of the enzyme N-acetyltransferase by light demonstrated that the response could be fitted to a visual pigment nomogram with a maximum sensitivity near 500 nm [23]. Almost identical results have been demonstrated in the pineals of several fish, reptiles and amphibians using a range of different assays of sensitivity, including melatonin release and electrical activity. An action spectrum for the deep brain photoreceptors mediating photoperiodic responses in quail was strikingly similar to the action spectra of pineal responses although the receptors involved were clearly not in the pineal [24,25]. These action spectra suggested the presence of opsin and 11-*cis* retinaldehyde within the pineal and basal brain.

In the pineal, antibodies against vertebrate visual pigment opsins have immunolabeled pinealocytes, and in the limited number of studies undertaken, chromophore (11-*cis* retinoid) has been isolated from the pineal of non-mammalian vertebrates (e.g. [26,27]). In contrast to the pineal, the identification of candidate photoreceptors within the basal brain has been difficult, with numerous studies over the past 25 years failing to provide an exact anatomical localization (e.g. [28]). However, three recent studies have suggested a location for these cryptic photoreceptors. Silver's lab demonstrated that cerebrospinal fluid (CSF)-contacting neurons within the septal and tuberal areas of the brain in the ring dove, quail and duck could be labeled with an anti-opsin antibody. Unfortunately, conclusive opsin identification was not possible in these studies because immunoblot analysis of the putative photoreceptor-containing brain regions failed to identify opsin-like proteins [29]. The second, and most detailed study to date, has been on the lizard *Anolis carolinensis*. In this species anti-opsin antibodies bound CSF-contacting neurons in the septal area of the brain. It should be noted that antibodies specific for mid-to-long wavelength cone opsins bound the CSF-contacting neurons while rod-opsin and short wavelength cone opsin antisera failed to recognize these cells. Immunoblot analysis showed that the anti-opsin antibodies recognized a single 40 kD protein in ocular, pineal and septal brain areas, but not in other areas of the brain. In addition, the anterior brain of *Anolis* was shown to contain specific retinoids associated with phototransduction [30]. A third study examined a 'primitive' vertebrate, the larval (Ammocoetes) lamprey. In this species, anti-rod opsin antisera labeled a population of CSF-contacting neurons within the basal brain (postoptic commissural nucleus and ventral hypothalamic nucleus), and in addition, antibodies raised against the alpha-subunit of retinal G protein (alpha-transducin) labeled the same cells [31]. Collectively these data suggest that a sub-population of CSF-contacting neurons, expressing mid-to-long wavelength cone opsins or rod opsins, are photosensory. We propose that these cells are the 'deep brain' photoreceptors that mediate extraocular and extrapineal photoreception in non-mammalian vertebrates. Molecular characterization of deep brain and pineal opsins is currently underway.

4. Conclusions

The photoreceptors that regulate circadian responses in mammals remain unidentified. Mice (rd/rd, rds/rds, rodless transgenics) in which visual responses are lacking show unattenuated circadian responses to light, demonstrating that the organization of visual and circadian light detection is quite different. Rod photoreceptors are not required, and if cone cells mediate circadian responses to light, then relatively few cells (even lacking outer segments) are sufficient to maintain normal sensitivities. Of the known opsins in the mouse retina, the mid-to-long wavelength sensitive cone opsin is the strongest candidate for photoentrainment, although we cannot currently preclude any involvement of the UV/blue opsin. In the blind mole rat, an animal with subcutaneous rudimentary eyes, lacking visual responses but showing photoentrainment, we find evidence for an opsin that is almost identical to the mouse red/green and human green cone opsins. Whether mammalian circadian responses to light are primarily mediated by cones or by a cone opsin in some unidentified retinal cell type remains to be determined. In addition, we cannot preclude the possibility that some novel 'circadian' opsin exists within the retina or that the rods may be involved at some level. Indeed, non-mammalian vertebrates employ extraretinal photoreceptors for photoentrainment, and preliminary

results suggest that both rod-like and cone-like opsins may mediate these responses.

Why the vertebrates should have evolved both visual photoreceptors and specialized extraretinal irradiance detectors remains a puzzle. It has been assumed that the task of irradiance detection would be 'simpler' using ocular photoreceptors, and that there would be no selective advantage in having extraocular photoreceptors. However this view ignores the differing sensory roles of vision and irradiance detection. Vision requires a focused representation of the environment; large numbers of photons need to be sampled in a fraction of a second in order to build a reliable image of the world. The optical nature of the eye achieves this precision, but in so doing prevents irradiance detection. The eye normally measures brightness in a particular point in space (radiance), not from the whole field of view (irradiance). For true irradiance detection light must be gathered from all directions and fall uniformly on an array of photoreceptors. This is exactly the effect achieved by having photoreceptors located within the brain. The tissues overlaying extraretinal photoreceptors scatter light to such an extent that all directionality is lost [25].

Lacking extraretinal photoreceptors, mammals are faced with the problem of how to achieve irradiance detection with ocular photoreceptors. This problem seems to have been solved by evolving anatomically and organizationally distinct projections to visual and circadian nuclei. Retinal projections to the visual centers of the brain show an extreme topographic order. A point on the retina will project to a precise positional map in the brain. By contrast, the retinohypothalamic projections lack this order, with ganglion cells across the retina projecting randomly to the SCN. This disruption of projections would result in a from of irradiance detection analogous to that achieved by a randomized optic fiber [32].

The work presented and reviewed in this paper emphasizes that photoreception in the vertebrates is complex and not limited to vision. All vertebrates have unrecognized and uncharacterized photoreceptor systems that play a fundamental role in the regulation of circadian and other autonomic physiological responses to light. An understanding of these photoreceptors is beginning to emerge, but we are far from being able to discuss the functional details and evolutionary relationships between visual and non-visual photoreceptors.

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