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Melanopsin: An Invertebrate Mechanism Incorporated into Mammalian Photoreception

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Abstract

There is a particular ganglion cell in the retina that responds to light in the absence of all rod and cone photoreceptor input, the intrinsically photosensitive retinal ganglion cell (ipRGC). The existence of this cell was predicted from observations over decades but not established till the 80s when it was shown that a novel photopigment, melanopsin, was expressed in a small subset of ganglion cells in the inner retina of rodents and primates. Phototransduction in mammalian ipRGCs more closely resembles that of invertebrate rather than vertebrate photoreceptors and is mediated by transient receptor potential channels. Through particular attributes of melanopsin, irradiance information is conveyed centrally via the optic nerve to influence several functions, including photoentrainment of the biological clock, pupillary light reflex, sleep, arousal states and some aspects of vision. Irradiance signals interface directly with the autonomic nervous system to regulate rhythmic gene activity in major organs of the body.

1. Introduction

Photoreceptors are the first in a chain of neurons that process visual information. In the lateral eye of vertebrates, light hyperpolarises rod and cone photoreceptors that synapse onto bipolar and horizontal cells in the first synaptic layer of the retina. The sign of the signal is either conserved or inverted in bipolar cells, resulting in chromatically dependent hyperpolarising or depolarising responses to visual stimuli. Visual information is then conveyed to the second synaptic layer for encoding and transmission to the brain by the ganglion cells.

Mammals rely on three ocular photoreceptors to sense light, rods, cones and ipRGCs. Rods and cones resolve a visual scene that allows us to interact in our environment in a conscious way. IpRGCs, through incorporation of an invertebrate opsin,

melanopsin, sense irradiance and integrate it over time and space to support non-image forming visual information. This feeds into the circadian system to allow subconscious adjustments of physiology relative to time of day and season. As the dominant species we believe that we are in control of our behavioural responses and the environment we find ourselves in through interpretation of information from our senses combined with cerebral knowledge and cultural learning but there are unconscious imperatives that must be met to maintain cellular homeostasis, and ultimately, survival.

Melanopsin provides the input, via ipRGCs, into the non-image forming visual system. The visual image and non-image forming systems have entirely different requirements. The image forming system requires rapid responses and uses a range of cone photoreceptors to discern wavelength in terms of colours and rods to provide images in dim light. The non-image forming system, on the other hand, produces a persistent response that integrates light over minutes and a chromatic integration that is wavelength dependent. This does not differentiate in terms of colour but is just as sensitive to different wavelengths of irradiance. This is achieved through photo equilibration of melanopsin between three states, two silent and a signalling state. I have termed this spectral interrogation.

2. Photoreceptors of the Parietal Eye

Early attempts by vertebrates to deal with the problem of spectral interrogation is illustrated by lizards who have non-image photoreception in an anatomically separate organ from the lateral eyes, utilising two opsins and G proteins. Unlike the lateral eye where complex neural circuitry, involving a range of different cell types performing initial visual-signal processing, information processing in the primitive parietal eye takes place in the photoreceptors which directly synapse onto ganglion cells. Solessio and Engbretson demonstrated that chromatic antagonism in the parietal eye originates in the chromatically dependent hyperpolarising or depolarising response of the photoreceptors to light. They suggest that the antagonistic nature of these responses provide lizards with a mechanism for enhancing detection of dawn and dusk [1]. The parietal eye of lizards is a simple yet highly structured photoreceptive organ that projects to non-visual areas of the mid brain (FIG. 1). Intracellular recording from these photoreceptors reveals antagonistic chromatic interactions already at this level. That is, the photoreceptors depolarise in response to green light and hyperpolarise to superimposed blue stimuli.

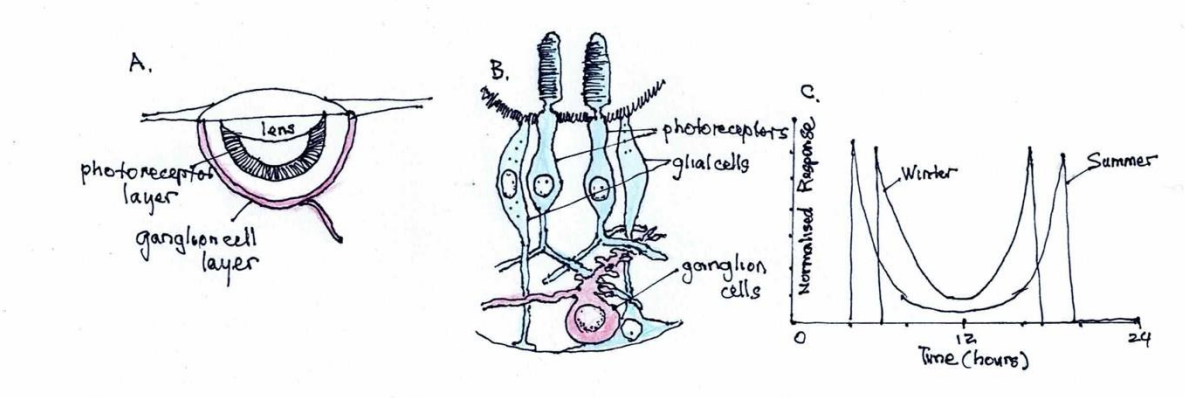

FIG. 1. **Anatomy and response of the lizard parietal eye. A. The parietal eye sits in a small foramen between parietal bones. The lens sits below a transparent skin layer. The photoreceptor outer segments project into the lumen between the lens and the retina. B. The retina has a single plexiform layer where the processes of ganglion cells and**

photoreceptors meet. Glial cells span the retina. C. Predicted steady-state membrane potential over the course of a summer and winter day in the environment of the lizard (X. vigilis). Both summer and winter solar spectra produce enhancement of light-dark transitions. Interestingly, these responses arise from ciliated cells typical of vertebrate photoreceptors and the two responses both arise from the same photoreceptor cell.

3. The Evolutionary Lineage of Phototransduction in Ciliary Photoreceptors

Su et al identified that the parietal eye photoreceptors resembled rod and cone morphology, but chromatic antagonism is unique amongst photoreceptors [2].

They found that the parietal eye photoreceptors contained two vertebrate opsins, pinopsin, a blue sensitive pigment, first identified in chick pinealocytes and a previously unidentified opsin, parietopsin, but subsequently also identified in fish and frog DNA databases. For comparison, they identified five lateral eye opsins in this lizard. The lateral and parietal eye expressed non-overlapping sets of opsins. The lateral eye opsins interact with G protein transductin. In pinopsin, instead of transducin, they found gustducin-α, and $G\alpha_o$ in parietopsin. G_o also mediates phototransduction in scallop photoreceptors, utilising SCOP2 visual pigment. Like parietopsin, SCOP2 is an ancient opsin that diverged early in opsin evolution. The G_o-mediated phototransduction pathway appears most ancient being present in vertebrates and invertebrates, coelomates, the last common ancestor. Later the ancestorial vertebrate photoreceptor acquired a second G protein, either gustducin or transducin for chromatic antagonism. The parietal photoreceptor evolved retaining these ancestorial features. Rods, cones and light-sensitive pinealocytes inherited only the gustducin/transducin-mediated pathway [3].

4. Identification of Non-Visual Pigments in Mammals

Diaz et al found that the photosensory system that synchronises the daily rhythms of food intake in chickens exhibits a high level of complexity, with retinal and extraretinal photoreceptor components contributing [4]. Retinal visual photoreceptors and those located in the pineal gland play a major role. Encephalic photoreceptors also contribute to entrainment of the circadian system in non-mammalian vertebrates [5].

In mammalian vertebrates, functional photoreceptors in the inner retina are responsible for driving diverse non-image forming activity through a circuit involving ipRGCs. This pathway appears to be an evolutionary conserved system for sensing light intensity and duration to assure the time-controlled organisation of physiology and, ultimately, survival.

Action spectra studies, such as pupillary light reflex (PLR) [6] and acute suppression of melatonin [7,8], suggested that these non-visual light-regulated responses were mediated, at least in part, by a different group of photoreceptors located within the inner retina and distinct from classical photoreceptors. A strong body of evidence showed that melanopsin (Opn4)-containing ipRGCs play a major role in photoentrainment, regulation of circadian photoperiod in response to constant illumination, PLR, photoinhibition of nocturnal activity and pineal melatonin synthesis suppression.

In terms of photosensitivity, IpRGCs are less sensitive than rods and cones, requiring longer exposure (minutes) and higher intensities with long lasting responses. The ipRGC response to a single photon is very slow with a prolonged integration time. (X20 for rods and X100 for cones). Long integration times allow summation of photons arriving seconds later, whereas this makes them insensitive to rapid variations in light intensity. These features make them well matched to detect ambient light over a long-time window [9].

5. Melanopsin Evolution

Melanopsin is highly conserved through evolution and was found in amphioxus and sea urchins demonstrating that deuterostomes have a melanopsin gene(s) [10,11]. Amphioxus melanopsin was investigated and found to be blue sensitive, λ_{max} 485 nm, bistable with G_Q activation efficiency close to G_q-coupled invertebrate visual pigments, also having a depolarising reaction in response to light, like invertebrate rhabdomeric PRCs.

Most non-mammalian vertebrates have more than two kinds of melanopsin, classified into two groups within the phylogenetic tree: Opn4x, the *Xenopus* ortholog gene and Opn4m, the mammalian gene [12]. Although non-mammalian vertebrates possess both, mammals have only one melanopsin gene. It has been suggested that, through the course of evolution, as mammals entered the nocturnal niche, they lost some visual opsins and Opn4x, likely a consequence of a chromosome re-arrangement [12].

The jawless fish, hagfish and lamprey (cyclostomes) express melanopsin, classified as Opn4m, the mammalian ortholog.

Based on several specification markers horizontal and amacrine cells in the inner retina could derive from a common ancestral photoreceptor progenitor with ipRGCs and be considered sister cells [13]. Horizontal cells have been shown to express Opn4x, together with clock genes (Bmal1 and Per2), the melatonin synthesising enzyme AA-NAT and a component of the non-visual photo cascade, G_q protein [14].

6. Photochemical Properties of Mammalian Melanopsin

Matsuyama et al exogenously expressed mouse melanopsin in cultured cells and spectroscopically studied its photochemical properties [14]. They found the photochemical reactivity was like squid rhodopsin with bistability and absorption coefficient typical of invertebrate bistable pigments. They suggested a potential allowance of wavelength-dependent regulation of melanopsin functions.

7. Melanopsin Spectrum

Light irradiation of melanopsin results in an increase in absorbance between 400 nm and 600 nm, with a similar spectrum to the dark state but with a higher amplitude. The photoreaction is indicative of formation of a protonated acid meta state called meta-melanopsin. This is characteristic of G_q-coupled opsins such as squid rhodopsin (FIG. 2).

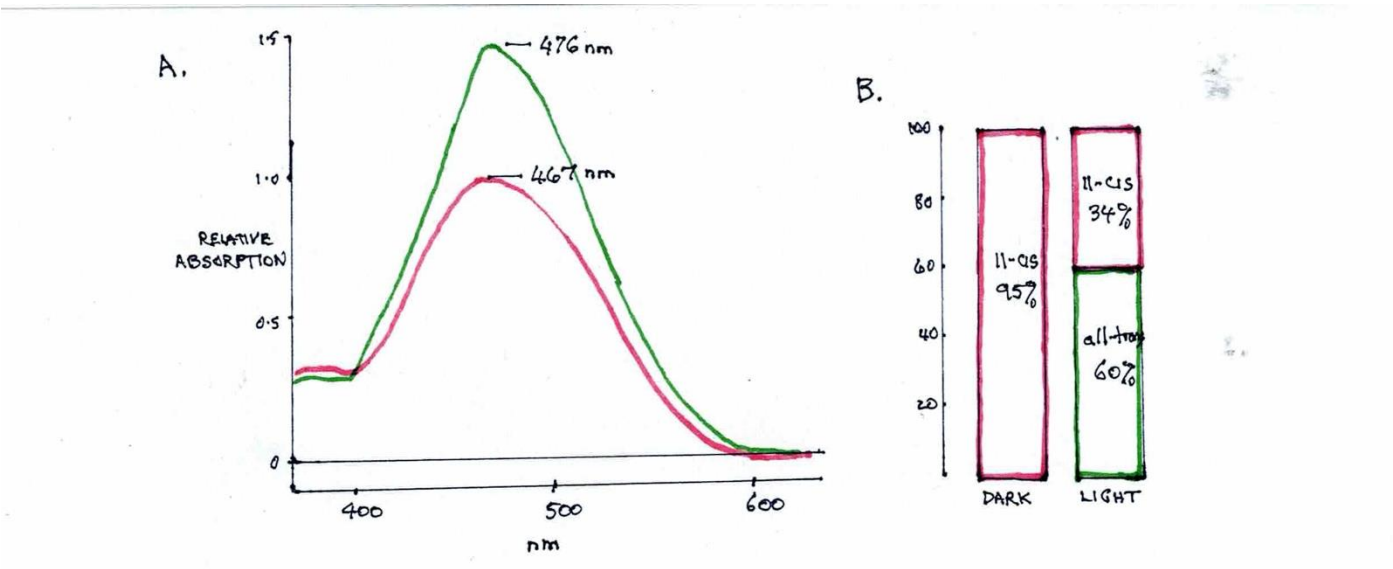

FIG. 2. **Spectra of melanopsin and meta-melanopsin. A. Model spectra of melanopsin, λmax 467 nm (red) and meta-melanopsin λmax 476 nm (green). Calculated by Matsuyama et al from their data using mathematical description of opsin spectra derived by Lamb [15]. The difference in amplitude between melanopsin and meta-melanopsin corresponds to the difference in the absorption coefficients of the two states. B. Calculated retinal composition in dark- and light exposed melanopsin (blue 448 nm light for 640 sec).**

8. Melanopsin bistability

G_q opsins function as bistable pigments [9,10], as opposed to bleaching or monostable pigments such as G_t opsins characteristic of vertebral visual opsins. Bistability confers an active state capable of reabsorbing a photon resulting in the re-isomerisation of retinal back to *cis*-retinal, reverting the activated receptor back to its resting state.

Irradiation at any wavelength, in the absorbance range of melanopsin, results in the formation of meta-melanopsin. After light exposure saturation, 11-*cis*-retinal is still present in significant amounts, light producing a steady state mixture.

They used acid denaturation to estimate the absorbance coefficient to melanopsin. They found that the absorption of pigment decays gradually as a new absorption peak is formed around 440 nm, upon acid treatment, indicating denaturation and formation of a protonated retinylidene Schiff base.

9. Extra-Melanopsin

When melanopsin is exposed to light, it produces meta-melanopsin manifest as an increase around 500 nm in the absorption spectrum, FIG. 1. However, when exposed to long-wavelength light (orange/red) a second peak occurs at 430 nm (represented by the blue trace in FIG. 2). Sustained irradiation increases the new peak and decreases the meta- peak. A new state emerges containing 7-*cis*-retinal called extra-melanopsin. This is probably formed from the meta-state because it would be unlikely that a photon could photoisomerise two double bonds. Extra-melanopsin can then be converted back to meta-melanopsin by short-

wavelength (blue) light irradiation. This indicates that melanopsin and extra-melanopsin can be freely exchanged by wavelength-dependent irradiation (FIG. 3).

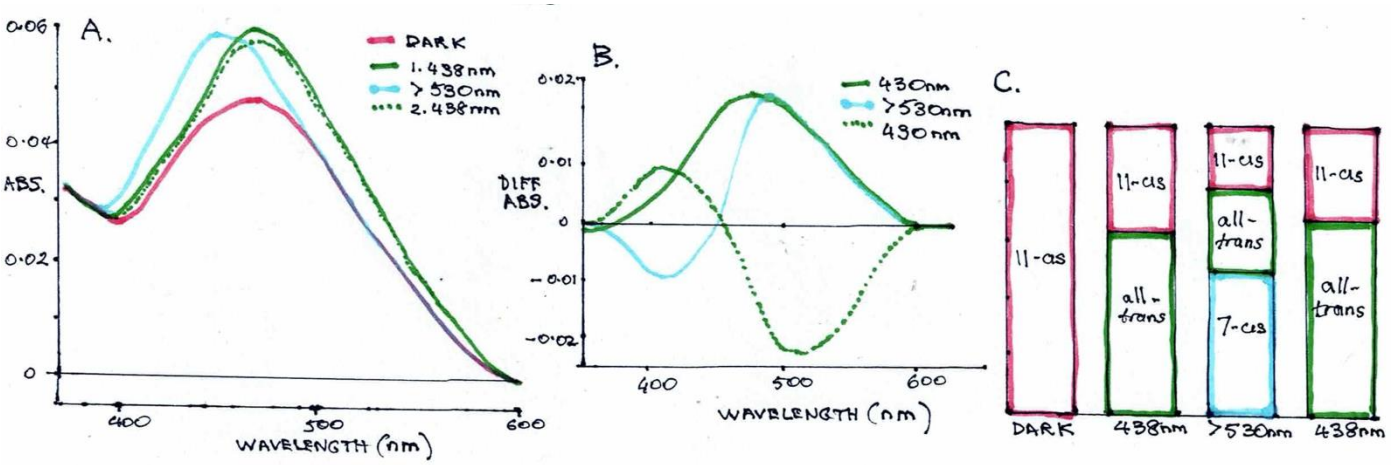

FIG. 3. **Extra-melanopsin forming under sustained irradiation with long-wavelength light and exhibiting bistability with meta-melanopsin. A. Melanopsin (red) exposed to 438(1) nm light for 160 seconds, achieving a photosteady state (green), like FIG. 1. The photosteady state mixture then exposed to >530 nm light for 1280 seconds until the mixture reached a new photosteady state (blue). Finally, the mixture was exposed to 438(2) nm again for 1280 seconds (stippled green). B. Difference spectra of responses to the respective light irradiations shown in A. C. Retinal composition of respective light exposure states. This showed that the photochemistry of melanopsin, even though it utilises a phototransduction cascade similar to that of the invertebrate rhabdomeric photoreceptors, is more complex than that for classical photoreceptors, giving the ipRGCs the ability to conduct different functions than those driven by rods and cones [14].**

10. Retinal Isomers

Rhodopsin is the visual pigment found in the rod outer segment of vertebrate and invertebrate photoreceptors, members of G_t and G_q signalling types of G-protein coupled receptors, respectively. The heptohelical membrane protein is composed of a light-absorbing 11-*cis*-retinal chromophore covalently bound to the ε-amino group of a lysine residue of an apoprotein (opsin) via a protonated Schiff base (PSB11) linkage. The positive charge of the chromophore is balanced by the negative charge of the glutamate counterion FIG. 4.

Considering that there are a range of isomers of retinal, 7-*cis*, 9-*cis*, 11-*cis*,13-*cis* and all -*trans*-retinal, why has 11-*cis* retinal been chosen by nature as the light sensing chromophore in visual pigments? The structure, stability, energetic and spectroscopy was examined by Sekharan and Morokuma using hybrid quantum and molecular mechanics [16]. Results showed that in both vertebrate (bovine, monkey) and invertebrate (squid) visual pigments the electrostatic interactions between retinal and the opsin dominated the natural selection of 11-*cis*-retinal over the other isomers in the dark state. They also found that 7-*cis*-retinal is an “upside-down” version of the all-*trans* isomer because structural rearrangements observed for 7-*cis*-rhodopsin from squid

was very similar to squid bathorhodopsin. The progressive red shift in the calculated absorption wavelength is due to the decreased bond length of the retinal.

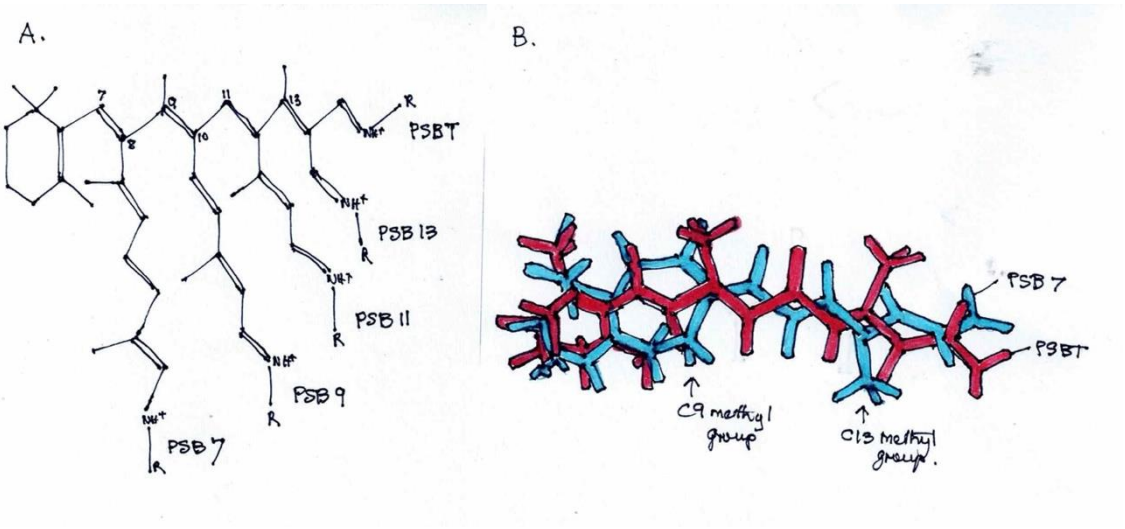

FIG. 4. **Schematic representation of retinal isomers. A. Comparison of 7,9,11,13-*cis* and all-*trans*-retinal. PSB, Pronated Schiff base; PSBT, all-*trans*-retinal. R refers to Lys-305 in squid and Lys-296 in bovine and monkey rhodopsin. B. Overlay of 7-*cis*-retinal (blue) and all-*trans*-retinal (Red). Although the Schiff base environment of PSB7 and PSBT are identical in squid rhodopsin, the geometric and spectroscopic properties of these two isomers are found to be opposite each other. In PSBT the C9 and C13 methyl groups point upwards, whereas in PSB7 they point downwards. PSB7 is an "upside-down" version of PSBT.**

11. Melanopsin Tristability

Melanopsin drives a transduction cascade that is distinguished by its prolonged time course. This makes it well suited to the integrative nature of non-image forming vision. Emanuel and Do investigate the signal integration by ipRGCs and found that, not only does the intrinsic light response integrate over minutes, but it also integrates over wavelength, a property not found in visual pigments. They found that light distributes melanopsin across three states, two silent and one active. Photo equilibration among states maintains pigment availability for sustained signalling. Stability of the signalling state permits minutes long temporal summation and spectral separation of the silent states promoting activation across wavelengths [17]. By broadening the tuning of ipRGCs in both temporal and chromatic domains, melanopsin tristability produces signal interrogation of irradiance for establishing patterns of gene expression that allow for anticipation and modification of physiology and behaviour in response to regular environmental cycles of time of day and season.

Their principal focus was the M1 ipRGC subtype because their melanopsin-mediated response was 10X greater in sensitivity and saturation amplitude than other subtypes. They were able to show the generation of a persistent response producing temporal integration in a window of ~5minutes. This response increased across stimuli until reaching saturation. They also found that the prolonged response arises from melanopsin phototransduction. This response resembles a feature of invertebrate photoreceptors 'the prolonged depolarisation afterpotential' (PDA). This arises from rhabdomeric photoreceptors, having a

stable signalling state. The pigment can be switched between signalling and silent states by light, either activating or deactivating the PDA. They measured the ipRGC action spectrum under dark adaptation, λ_{max} 471 nm and again with 600 nm light (a wavelength minimising persistent response) and found the spectrum was blue shifted to λ_{max}453 nm, indicating a pigment state distinct from that of darkness. These experiments indicated that melanopsin activates from more than one state and is therefore not bistable. With 440 nm background light (a wavelength producing a large persistent response) ipRGCs exhibited an action spectrum that was broader than that of a single pigment state. Collectively, their data suggested that ipRGC's action spectra reflected one pigment state, another or both depending on the conditions of illumination. Melanopsin was activating from two states they referred to as cyan (λ_{max}471 nm) and violet (453 nm). Equivalent activation from cyan or violet states, separated by ~20 nm, broadens the wavelength tunning of ipRGCs. This spectral separation is equivalent to that from red (λ_{max}552 nm) and green (530 nm) cone pigments.

Here the separation exists within a single pigment. Their conclusion was that melanopsin has two silent states and one signalling state, in other words tristable. These findings agree with Matsuyama et al whose study demonstrated a ground state (λ_{max}467 nm containing 11-cis-retinal), photo equilibrating with a meta-signalling state (476 nm, all-trans-retinal), but also a third extra-state (446 nm, 7-cis-retinal) [14]. A physiological role was hypothetical and controversial because 7-cis-retinal was not thought to exist in nature due to energetic constraints. By comparison, the approach of tristable melanopsin to photo equilibration is slower than bistable Drosophila rhodopsin consistent with the integrative nature of non-image forming vision as compared to image forming vision.

12. Photic Memory

Mure et al found that prior light exposure alters the subsequent pupil response to light (FIG. 5). Prior exposure to adapting long wavelength red light (620 nm) caused a significant increase of 28.2% in steady-state equilibrium response, whereas a prior blue light (480 nm) caused decreased responsiveness by 21.4%. They interpreted this as a form of rapid and reversible "photic memory" since information of the prior spectral light conditions is retained and shapes the subsequent response to light.

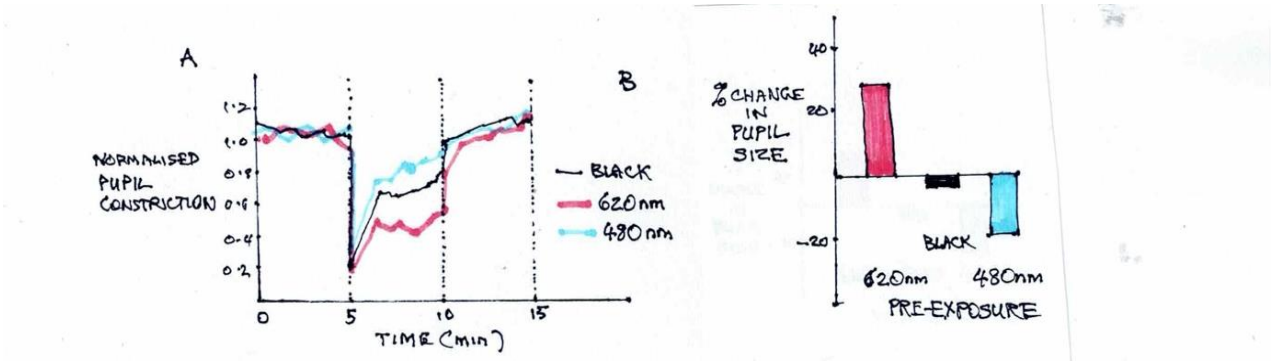

FIG. 5. **Alterations in steady-state equilibrium pupillary reflex response following pre-exposure with monochrome lights. A. Responses of subjects after pre-exposure to 5 minutes adapting 620 nm (red line), 480 nm (blue line), compared to normalised dark adapted reference response (black line). B. Histogram summarising alteration in steady-state pupil responses.**

13. Photopigment for Ancient Functions

One of the characteristics of the vertebrate retina is the presence of a variety of non-visual opsins in addition to the classical opsins, Opn1 and 2, which have been shown to be expressed in the inner retina. Opn 3,4 and 5, retinal G-protein-coupled receptor (RGR) and peropsin [5,19]. Melanopsin (Opn4) was first identified from the intradermal melanophores of the frog *Xenopus laevis* [20] and is found in a broad range of mammalian and non-mammalian vertebrates including humans. Melanopsin and invertebrate G_q-coupled visual opsins share a close phylogenetic relationship, both groups belong to the G_q subfamily of opsins. Based on amino acid sequence, melanopsin exhibits higher levels of sequence similarity with invertebrate rhodopsin than vertebrate visual opsins.

It has been clearly shown that melanopsin acts as the photosensitive molecule in ipRGCs and is involved in non-image forming activities. Pupillary light reflexes (PLR), light-entrainment of circadian rhythm activity and melatonin suppression [21-23].

In addition to non-image forming functions, melanopsin in the retina of primates may also modulate visual processing, fine tuning visual pathways depending on time of day [24,25]. It has been found that there is some heterogeny shown in the morphology of ipRGCs. Defined subtypes have been identified with variation in their ramifications within the retina and to their projections to specific brain areas [25-28]. Although ipRGCs are a small minority of mammalian ipRGCs (<10%), they form an expansive photoreceptive net in the inner retina [29].

This bilayer photoreceptive net is anatomically distinct from the rod and cone photoreceptors of the outer retina. As well as formally characterised M1 and M2 cell subtypes, there are bistratified M3 cells and M4 cells which exhibit a large soma size and dendritic fields. The large sparsely branched dendritic arbours of M1 cells have been shown to monostratify at the outer limit of the OFF sublayer of the inner plexiform layer (IPL), whereas M2 cells which also have similar arbours but ramify within the ON sublayer of the inner third of the IPL [27,28] (FIG. 6). Some of these cells support spatial visual perception in mice [26]. In relation to this, although ipRGCs were shown to regulate non-image forming subconscious functions there is increasing evidence that ipRGCs project to all major retino-recipient regions and their influence may extend to regulation of perceptual vision, providing environmental information that may assist multiple visual processes [29].

In this respect, amacrine and bipolar cells transmit inputs to ipRGC neurites, providing an anatomical link by which ipRGCs may modulate visual pathways [30]. Opn4 also appears to be involved in modification of the core visual pathway in humans in response to light exposure of long duration [31]. It has been shown that primate ipRGCs combine with visual photoreceptive cell mechanisms to encode irradiance over the whole visual spectra range [22]. The role of ipRGCs in the retina has now been extended to include not only the modulation of visual processing but also contrast detection and light adaptation [32,33].

IpRGC project directly to the SCN and sends projections to the intergeniculate leaflet and olivary pretectal nucleus which are both involved in modulation of circadian rhythm and PLR [34], as well as the ventral paraventricular zone and ventrolateral preoptic nucleus, brain areas involved in sleep control and circadian locomotion (FIG. 7). It has even been found that non homologous Opn4 expression in cultured cell lines renders non-retinal cells light-responsive [35,36]. It has become clear that models of vision in the future will need to include input from the melanopsin driven photoreceptive system of the inner retina.

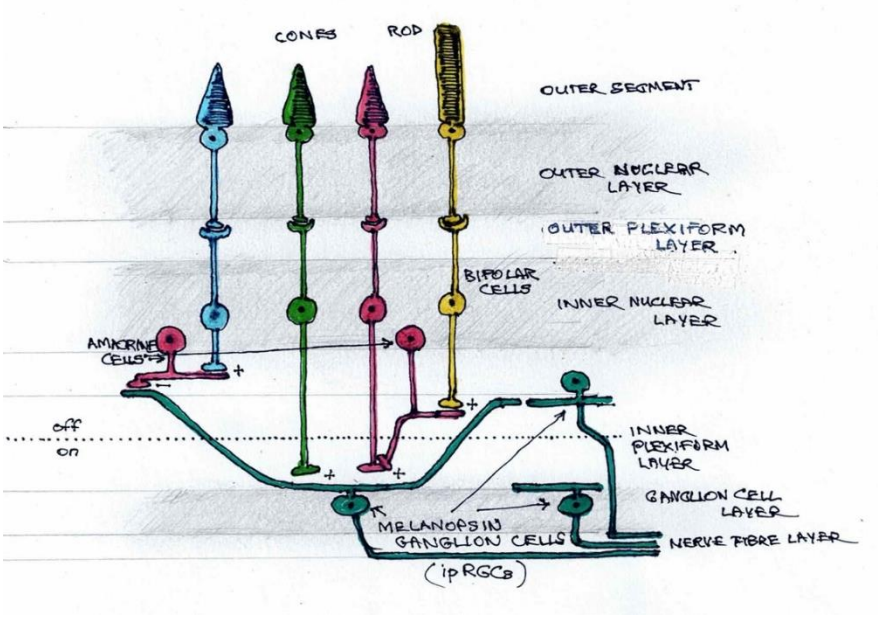

FIG. 6. **Synaptic circuitry of melanopsin-expressing RGCs in the retina. IpRGCs are mainly located in the ganglion cell layer, the rest are displaced to the inner nuclear layer. They have sparse dendrites but extremely large dendritic fields. These dendrites arborise in the inner plexiform layer (IPL), forming a major plexus in the outer most boundary of the IPL and a minor plexus in the inner most boundary of the IPL. Green and red cones provide excitatory inputs through bipolar cells to ipRGC proximal dendrites. Rod cells also provide excitatory inputs through rod bipolar cells, type II amacrine cells and cone bipolar cells successively. Blue cones provide inhibitory inputs through cone bipolar cells and inhibitory (GABAergic) amacrine cells. +, excitatory input; -, inhibitory input.**

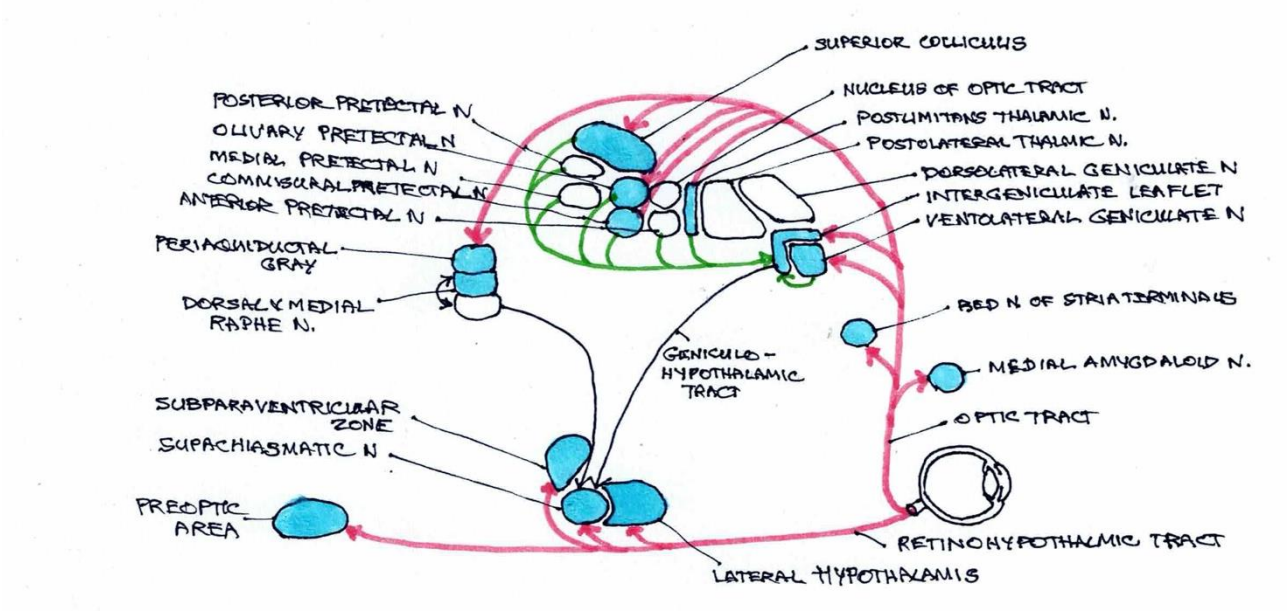

FIG. 7. **Schematic representation of fore- and midbrain projections of the rodent retina. IpRGC targets- blue regions and red lines. Non-visual projections to intergeniculate leaflet-green lines. All other brain regions are retinorecipient but not necessarily from the ipRGCs.**

14. Melanopsin's Advantages for Non-Image Vision

Photo equilibration of melanopsin among signalling and silent states supports sustained activation of ipRGCs by maintaining available pigment molecules for activation. By contrast, monostable rod and cone pigments spontaneous dissociate after a single activation, thereby loosing photosensitivity. Because pigment regeneration requires a series of reactions in accessory cells there is a limited capacity for sustained signalling [37]. Emanuel and Do's observations of the violet state (E state of Matsuyama et al [14]) and its activation provide evidence for light-driven regeneration of melanopsin in ipRGCs, which is important because ipRGCs express relatively few melanopsin molecules but must capture photons continuously over long timescales for non-image visual responses [38,39]. Tristability is unique in that it displays a similar activity level across a variety of broadband spectra, 'spectral invariance', with a broad range 'state purity'. Bistability can provide one or the other, but not both. State purity facilitates fine-tuning of pigment function translated into physiological and metabolic response. The balance between activation and de-activation can be altered by expression of screening pigments, upstream of photoreceptors, a strategy used by many species for adaptation to different environments. Spectral sensitivity is broadened by activation from two silent states, conferring wavelength integration. Melanopsin approaches state equilibrium with an extended time course, which imposes a low-pass filter on visual signals, ideal for the integrative nature of non-image vision.

15. Conclusion

Melanopsin belongs to the group of opsins that include the visual pigments of cephalopods and arthropods (G_q opsins), typical of invertebrate visual photoreceptor cells. We possess both vertebrate and invertebrate types of photoreceptor molecules. The vertebrate image forming visual opsins have been extensively studied and are well understood. Less so the G_q opsins, however, it is clear that image and non-image visual systems have different requirements, and this is reflected in the features of the different opsins and the information they collect and transmit. As previously stated, the ipRGCs integrate some input from the rods and cones, recent evidence indicates that the information sharing may be reciprocal.

If analogous physiological phenomena result from the incorporation of melanopsin in mammal visual systems, then one can take advantage of its spectral interrogation to more precisely assess the spectral composition of a light source to specify photoentrainment and the impact it has on the modulation of other light-dependent circadian phenomena. This autonomous system contains incredible wisdom developed over eons to protect survival of the species. The system is accessed through the individual being exposed to changes of irradiance at dawn or dusk, regularly, to allow it to be entrained. How often does this happen to a population in an urban environment?

16. Future Directions

The sensory task of irradiance detection and non-image vision is not trivial, as demonstrated in mice, where messaging to the SCN commences at birth, whereas photosensitivity of the image forming pathway is only detected from postnatal day 10, just before eye opening [13]. Most life forms display a rhythmicity of physiological response coordinated with cyclic irradiance patterns determined by the movement of our planet. The ubiquity of these rhythms makes it obvious that this is fundamental to survival of all species. Dysregulation of the circadian clock is implicated in a range of human disorders. Behavioural, including

sleep patterns, metabolic (cardiovascular, obesity, diabetes), migraine and cancer. Yet, we continue to disregard these imperatives with our sophisticated urban lifestyles and industry. Despite the progress of modern medicine these medical conditions are becoming more rather than less prevalent. The way forward may be to heed the rhythms of nature and return to a more sustainable form of civilization rather than relying so heavily on technological innovation to control human disease.

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