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RESEARCH ARTICLE

Melanopsin and the influence of inner retinal photoreception

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Almost all species exhibit daily cycles of physiology and behaviour driven by an endogenous rhythmicity. This clockwork only provides a selective advantage when synchronised (entrained) to external time, measured by the repetitive, daily rotation of the earth on its axis and its annual movement around the sun. Humans have been traditionally considered to be a diurnal species, active in daylight and inactive with night but with the advent of urban living and artificial sources of lighting these rhythms of evolutionarily adapted patterns of behaviour and metabolism are being disturbed and redistributed. The disharmony is strongly expressed with shift-workers having higher rates of obesity, diabetes, metabolic syndrome and possibly prostate and breast cancer. Can these changes in human behaviour also be reflected more subtly in increasing rates of disease and cancer throughout the community. As a skin cancer clinician see an increasing diagnosis of melanoma, particularly. Does this represent maladaptive patterns of sun exposure. This certainly seems to be the case with recreational, rather than occupational exposure patterns.

Gross changes in illumination at twilight, dawn and dusk, are the zeitgebers that entrain the endogenous clockwork, the circadian system. What percentage of the population regularly observe these changes of light and how influential is this on our well-being?

Photoreception in vertebrates

In non-mammalian vertebrates, the photoreceptors responsible for entrainment of the clock are often extraocular. Located in specialised organs of the central nervous system (pineal and parapineal glands and the parietal eye of lizards), parts of the brain itself and distributed through other non-neuronal organs and tissues. A distinct sensory modality quite separate from which is traditionally considered to be the visual system. Mammals, however, rely exclusively on ocular photoreceptors. A distinct component of the optic nerve, neurons of the retinohypothalamic tract, leave the optic nerve at the chiasma and travel directly to the suprachiasmatic nucleus, the master controller of the circadian rhythm, located within the hypothalamus.

Melanopsin and the intrinsically photoreceptive retinal ganglion cells

Until recently, all mammalian ocular photoreceptors were thought to be either rods or cones but persistence of circadian rhythmicity in mice with progressive outer retinal degeneration and almost no rod or cone function[1-4] suggested otherwise. Also, blind human subjects were found to retain circadian light responses[5]. Transgenic mice, lacking rods and cones, retained circadian entrainment and other light related reflexes with sensory characteristics (threshold sensitivity, response kinetics and spectral sensitivity) quite different from rod and cone photoreceptors. The answer is that there is a small subset of the retinal ganglion cells of the inner retina that are intrinsically photosensitive (ipRGCs). Interestingly, their photopigment showed a greater structural similarity to invertebrate rhodopsin, rather than rod and cone opsin, and a phototransduction cascade resulting in a depolarising response to light. Most of the genes encoding extra-ocular non-mammalian photoreceptors had been lost from the mammalian genome, the exception is melanopsin, a pigment initially isolated from the photosensitive melanophores in the skin of a frog, *Xanopus*[6]. A melanopsin orthologue was found in both mice and human genomes and was also found to be expressed in this subset of retinal ganglion cells[7]. It was also found that some of these ipRGCs provided visual information to the circadian system[8].

Work by Berson et al[9] and Hatter et al[10] further defined their characteristics but at this stage projections to the dorsal lateral geniculate nucleus (dLGN), the origin of thalamocortical projections neurons, could not be defined, appearing to exclude them from the central pathways responsible for image-forming vision. It was clear that ipRGC were responsible for a range of reflex and subconscious light responses, such as the pupil light response (PLR) and inhibition of melatonin production. Its role now, however, includes provision of photic information to the sleep/wakefulness system[11-15], modulation of cognition[16] and aspects of photophobia and photoallodynia[17-19], expanding the concept to a non-image forming (NIF) visual system, with the ability to adjust physiological and behavioural responses according to the level of ambient illumination.

Another feature of invertebrate rhodopsin, shared with melanopsin, is bleach resistance. Berson et al[9] originally reported that ipRGC's light response persisted under bright and /or extended light exposure. This is achieved in rhodopsin by retaining *all-trans* retinal following light absorption and using a second photon to regenerate the *cis* isoform. This ensures a portion of the opsin binds *cis*-retinal and can detect further light exposure, even under extended and intense illumination.

IpRGCs have extensive dendritic trees in the inner plexiform layer (IPL), which are not only a site of their own phototransduction, but they also receive synaptic input from bipolar and amacrine cells, accepting visual information originating from rods and cones[20-24]. Melanopsin becoming increasingly influential as light becomes brighter and more sustained and rods are approaching saturation. Their predominant role, however, is encoding steady state illuminance to track diurnal variation in light intensity.

Heterogenicity of intrinsically photoreceptive ganglion cells

The original description of ipRGCs applied to the dominant M1 subtype, having the strongest melanopsin expression and major projection to the SCN. However, it has been found that there are 5 subtypes able to interact with horizontal, amacrine and bipolar cells, their varying morphology supporting diversity in inter-retinal connectivity and revealing a more extensive projection to retino-recipient regions including the dLGN. As the dLGN is the relay station for visual input to the cortex, presenting the possibility that ipRGCs are directly contributing to perceptual vision. The melanopsin-driven light response has low sensitivity and poor temporal fidelity, so it is unlikely to contribute to high acuity visual patterning. Data suggests that it has a role in helping the dLGN encode ambient illumination[25] and judge spatial brightness[26].

Intraretinal signalling between photo - receptors, ganglion cells and interneurons

Retinal dopaminergic amacrine neurons (DANs) play a central role in modulating retinal function determined by prevailing illumination conditions. They can produce sustained light responses characteristic of melanopsin phototransduction and are driven by cationic currents

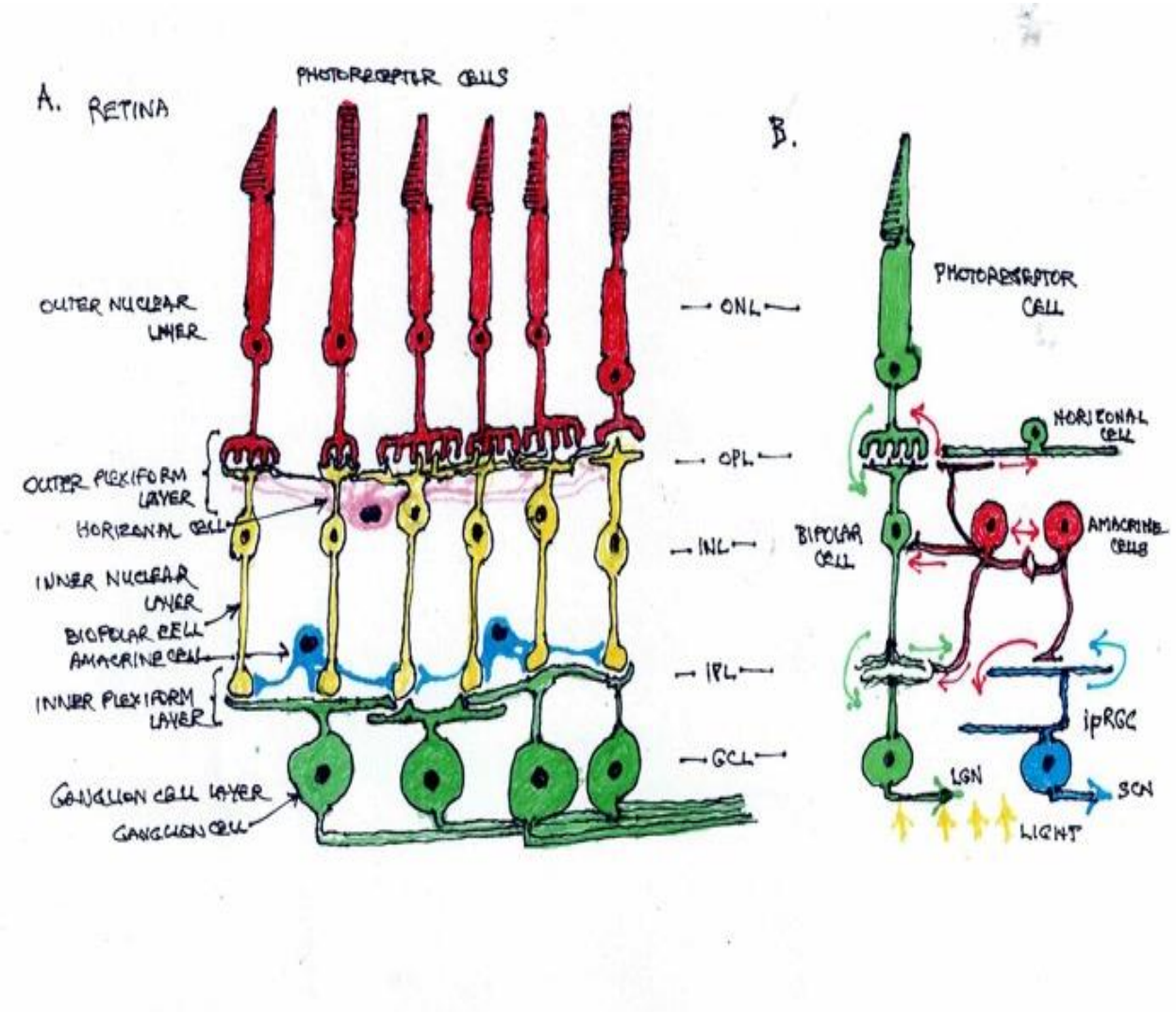
A. RETINA
PHOTORECEPTER CELLS
OUTER NUCLEAR LAYER
OUTER PLEXIFORM LAYER
HORIZONAL CELL
INNER NUCLEAR LAYER
BIPOLAR CELL
AMACRINE CELL
INNER PLEXIFORM LAYER
GANGLION CELL LAYER
GANGLION CELL
ONL
OPL
INL
IPL
GCL
B.
PHOTORECEPTOR CELL
HORIZONAL CELL
BIPOLAR CELL
AMACRINE CELLS
ipRGC
LGN
SCN
LIGHT

Figure 1

thought to have originated from ipRGCs. This features long latency, post-stimulation persistence and a peak spectral sensitivity at 478nm. These sustained, but not transient responses, persist in rod and cone degenerated retinas. There is co-ramification of ipRGC dendrites and amacrine cell processes in the inner plexiform layer (IPL) and this is thought to produce a counter-current of information flow, against the canonical photoreceptor to ganglion cell drive, informing the system of illumination conditions to modify retinal response.

The flow of information in the retina is traditionally thought to be from rods and cones of the photoreceptor cell layer in the outer retina to the inner ganglion cell layer and then to the brain with various cells, including the amacrine cells, acting as interneurons.

This has been investigated and it has been found that there is information flow from the ipRGCs to the rod and cone photoreceptors, going against the normal flow of current, by way of the DANs[27]. Co-ramification of ipRGC dendrites with DAN processes in the IPL providing the anatomical pathway and ultimately modifying the retinal response according to conditions of illumination.[20,23,28]

It has been found that glutamate is released from the dendrites of light activated glutaminergic ipRGCs acting on receptors on co-stratifying processes of DANs in the outer most segment of the IPL. Retinal dopamine, released by DANs modify the function of all major classes of retinal neurons, including photoreceptors, horizontal and bipolar cells in the outer retina, reversing the direction of visual signalling. In contrast to the fast, spatially discrete forward feeding pathway this feedback signalling is slow, modulatory and is a consequence of the spatially diffuse, wide ranging cell processes of both DANs and ipRGCs.

This confirms that information flow in the retina is bi-directional and that ganglion cell photoreceptors act as both interneurons for intraretinal visual signalling as well as projection neurons transmitting visual signals to central visual nuclei.

Photoreceptive cells (PRCs), bipolar and horizontal cells make synaptic contact with each other in the outer plexiform layer (OPL), whereas, bipolar, amacrine and ganglion cells make contact in the inner plexiform layer (IPL).

The vertebrate retina contains an endogenous oscillatory mechanism that temporarily controls biochemical, physiological and genetic functions.

A strong body of evidence shows that retinal cell layers contain autonomous oscillators capable of generating daily rhythms in the synthesis of melatonin, lipids, cAMP, expression of clock genes, photopigments, enzymes and neurotransmitters involved in a variety of physiological visual and non-image forming functions.

A. Structural organisation of the mammalian retina.

Outer nuclear layer- rod and cone photoreceptor cell bodies
Outer plexiform layer- synaptic connections between rods, cones, bipolar and horizontal cells
Inner nuclear layer- horizontal, bipolar and amacrine cell bodies
Inner plexiform layer-amacrine, bipolar and ganglion cell synaptic connections
Ganglion cell layer- both conventional and intrinsically photosensitive retinal ganglion cell bodies and neuronal output of the retina, making up the optic nerve.
Conventional ganglion cells innervating the lateral geniculate nucleus (LGN), the thalamic visual nucleus of the brain, and melanopsin-driven ganglion cells innervating the suprachiasmatic nucleus (SCN), the hypothalamic master biological clock nucleus

B. Neuronal circuit of light input pathways in the mammalian retina.

Green arrows- Signals from rods and cones to ganglion cells through ON-bipolar cells to dopaminergic amacrine cells and lateral geniculate nucleus (LGN).
Blue arrows- signals from ipRGCs to dopaminergic amacrine cells and the SCN.
Red arrows- dopamine diffusion to cells in all retinal layers.
Yellow arrows-light entering the retina, passing through the retinal cell bodies and their processes.

Light and cognition

It was initially thought that non-image forming vision did not project to cortical levels of brain function. This is now obviously not the case. Data indicates that ambient light modulates brain function and cognition. Light is essential for many visual cognitive tasks, but it also modulates non-visual functions, including alertness and performance of cognitive tasks[29,30]. As a diurnal species behavioural and physiological functions vary with circadian rhythmicity such as sleep-wake cycles, hormonal secretions, thermoregulation and gene expression. This circadian rhythmicity also affects cognitive processes-attention, executive function and memory[31-33].

Light modulation of brain responses by neuroimaging

Neuroimaging studies were used to identify how brain activity, using non-visual auditory tasks, was modulated by light exposure[34-37]. Effects on cognition were aimed specifically at auditory perception, attention, executive function and working memory. PET investigated the effects of light at night and fMRI the effects of light exposure during the day. They investigated sustained, rather than visual transient responses, using uniform irradiance devoid of spatial structure and monochromatic light of varying wavelengths, all aimed at detecting non-visual effects of light.

Light-induced changes in the performance of non-visual cognitive tasks were detected with neuroimaging and demonstrated in multiple areas, including alertness-related subcortical brainstem activity, located in the locus coeruleus[37]; the hypothalamus, in the suprachiasmatic nucleus[34]; dorsal and posterior thalamus[35-37]; but also, in long term memory and emotion-related areas such as the hippocampus[35,37] and amygdala[37]. At the cortical level, in areas involved in top-down regulation of attention: the dorsolateral prefrontal cortex, intraparietal sulcus and sub parietal lobule[34,36]; as well as areas involved in bottom-up reorientation of attention including the right insula, anterior cingulate cortex and superior temporal sulcus[35,36]. The left frontal and parietal cortex implicating working memory.

Functional MRI showed wavelength-dependent changes during higher executive tasks, blue light (~480nm) enhanced brain responses, or, at lease, prevented decline associated with green and violet light effects. This blue light enhancement matched wavelength-dependent behavioural effects of light also matching the peak spectral sensitivity of melanopsin. This suggests that the melanopsin-driven ipRGCs have a dominant effect in non-visual modulation of brain activity.

Distribution of response

Distribution of non-visual effects of light relate to exposure duration and intensity. Longer duration and/or higher intensities trigger larger and longer lasting modulation of task-related responses[34,35]. Subcortical regions expressed swift and transient response, triggered by weaker stimuli, while modulation of cortical activity required stronger and more sustained simulation. The exception was the response of the limbic system.

Hippocampal and amygdala responses were immediate. The amygdala receives direct input from ipRGCs[38] and indirectly through the superior colliculus and thalamus[39]. The amygdala projects directly to the hippocampus, which also receives input form the brainstem[40]. This raises the possibility that blue light favours an early affective and memory-related arousal, prompting more immediate behavioural adaptation to changing environmental conditions.

Conclusion

What is the significance of non-image visual information gathering as far as the skin is concerned, particularly in relation to melanoma risk assessment? Irradiance detection notifies the central nervous system of time of day which is highly significant in terms of risk and danger of exposure to UVR. Change of light at dawn entrains the intrinsic circadian system and encourages onset of activity. This is defensive in as much as allowing for initiation of activity with the sun low to the horizon and exposure to longer wavelengths of light. So, not only is there exposure to solar radiation with a lesser UV component but this also allows for conditioning of the skin during a low-risk time frame in preparation for potential exposure with the sun more overhead.

Man is designed to be exposed to solar radiation but to achieve any level of self-protection this exposure must be regular to maintain protective effects. Melanoma has been found to be more common in in-door workers rather than out-door workers. The out-door worker has a more regular exposure pattern. Obviously, for the very fair-skinned individual these self-protective mechanisms are less effective because of an incomplete tanning response due to genetic deficiency in the melanocortin1receptor on the melanocyte. This can be compensated for with hat, clothing and sunscreen but this protection is incomplete, and a level of risk remains.

The other feature of melanoma, that separates its exposure pattern from non-melanoma skin cancer, is its predilection for intermittently exposed skin, being more common on the back and shoulders. Self-protective processes seem to require a level of exposure. Early morning recreational exposure appears to be optimal particularly for the in-door worker and activities with a maximal amount of skin exposure may also be helpful. Can the skin sense light? This question remains unanswered, but the skin contains the full range of functional opsins and transductory components. As stated, all photosensory information

gathering appears to be ocular in mammals. The photosensory capacity of the skin needs to be further investigated to help unravel our intrinsic self-protective mechanisms and eventually inform patterns of exposure more coordinated with our unconscious self-protective physiology.

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Conflicts of Interest

None

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