

For humans, vision is the sense that dominates over all others. Our interactions with the external world, and with each other, rely heavily on what we see - or at least on what we believe we perceive. Small wonder that so much of the brain is devoted to visual processing, and that damage to the visual system often leads to profound disability.

In this edition, we start a series of primers on Visual Neuroscience, written by experts in the fields of retinal physiol-

ogy, the anatomy of the visual pathways, colour vision, eye movements, visual illusions and attention. The aim of this series is to convey not only the fundamentals, but also to update readers on new and exciting developments in these fields.

Research in vision moves at an extremely fast pace, as exemplified by the new findings reviewed in our opening primer on the retina. In the last few years there has been a quantum leap in

this field with the discovery of a completely new visual-sensing system that is entirely different from the classical rod and cone system. The characterisation of this novel pathway has only just begun but the findings suggest it may play a critical role in the control of circadian rhythms.

In subsequent issues, we hope to bring you up to date on a range of old and new findings in vision. We hope you will enjoy what you see.

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The Neural Retina: Three Channels of Light Detection

The retina is a neural network that has two critical functions: transduction of light into an electrical signal and the vital initial processing of visual information. Phototransduction is achieved by specialised sensory retinal neurons: The cone photoreceptor cells for bright light vision, the rod photoreceptor cells for dim light vision and the recently discovered intrinsically photosensitive melanopsin ganglion cells which have a role in irradiance detection for non-image-forming tasks. Here we will outline these three light sensing retinal channels, focusing on their principal functional features.

Basic Retinal Anatomy

A remarkable feature of the vertebrate retina is its highly ordered neuronal organisation. The retina is composed of 3 cellular layers interspersed with two synaptic layers (Figure 1; e.g.^{1,2}). The soma of the rod and cone photoreceptor cells resides in the outer nuclear layer. The inner nuclear layer contains the soma of the bipolar cells, the horizontal cells and the amacrine cells. Some amacrine cells are displaced to the ganglion cell layer, which principally contains the soma of the ganglion cells. The rod and cone photoreceptors utilise multiple parallel cellular pathways to relay the light signal to the ganglion cells, the output neurons, whose axons form the optic nerve and mainly project to the lateral geniculate nucleus and the superior colliculus. Recently, a novel class of ganglion cell has been identified that does not require rod and cone input to generate a light signal. These cells form an unexpected additional light sensitive channel in the retina and their axons project primarily to the suprachiasmatic nucleus and the pretectal nuclei.³⁻⁵

The Cone System

Photopic vision begins at the cone photoreceptor cells. The structure of these sensory neurons is optimised to maximise photon capture, with an elongated outer segment region packed with membranous discs embedded with either long- (LW), medium- (MW) or short- wavelength (SW) sensitive opsin photopigment (see chromaticity section). The process of phototransduction is initiated in the outer segment. Absorption of light by 11-cis retinal in the photopigment binding pocket activates a G-protein cascade

that is negatively coupled to a cGMP-gated cation channel. Therefore during light stimulation the channels close and there is a decrease in the influx of cations into the cell. This results in a graded membrane hyperpolarisation and reduced glutamate release from the cone synaptic terminal.

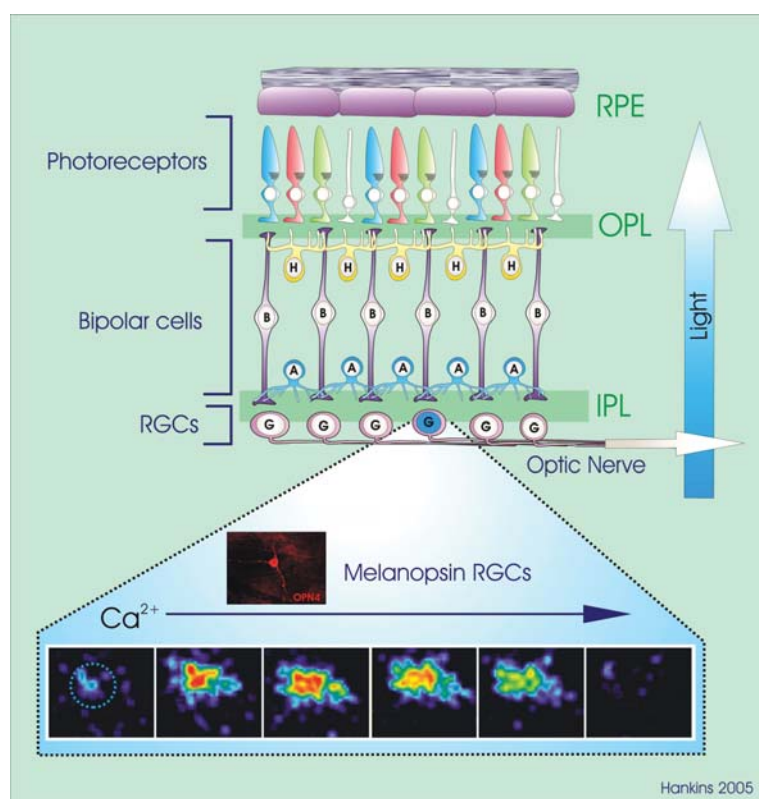
The light signal is transmitted through the retinal network to the output ganglion cells. The cones make synaptic contacts at the outer plexiform layer with bipolar cells. Two main sub-types of cone bipolar cell are present: OFF-centre and ON-centre cells. The OFF cone-bipolar cells hyperpolarise in response to light and the ON cone-bipolar cells depolarise upon retinal illumination. These cells segregate the light signal into ON- and OFF- channels. Therefore, ON-ganglion cells fire action potentials in response to increases in retinal illumination whereas the OFF-ganglion cells respond to decreases in the illumination level. The cone to bipolar to ganglion cell pathways represent the direct route of signal transmission through the retina and form the 'vertical' retinal pathways.

Contrast. In addition to the vertical pathways, lateral pathways in the retina further process the light signal. One such system involves the horizontal cells. The horizontal cells receive inputs from several photoreceptor cells that

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The neural retina is a network of neurones in contact with the retinal pigment epithelium (RPE). Classical photoreceptors (rods and cones) synapse at the outer plexiform layer (OPL). Here, bipolar cells (B) take the rod and cone signals and feed them forward to the inner plexiform layer (IPL), forming contacts with retinal ganglion cells (G), whose axons form the optic nerve. At the OPL and IPL, horizontal cells (H) and amacrine cells (A) are respectively interneurons that sub-serve lateral signal processing. Inset: a subpopulation of retinal ganglion cells (blue) expressing melanopsin, are intrinsically photosensitive and signal irradiance information to a range of retino-recipient brain areas. Calcium imaging experiments⁵ reveal a network of light responsive cells in the inner parts of the mammalian retina.

surround a central group of cones and this information is fed through to the bipolar cells. Importantly, the lateral input signal is opposite to that of the vertical pathway signal thereby producing a 'lateral inhibition' effect. Therefore the receptive fields of ON- and OFF- bipolar cells have two components: a centre and a surround. Illumination of the central area of a bipolar cells receptive field results in an ON- or OFF- centre response, whereas illumination of the peripheral receptive field results in the opposite ('opponent') response. This feature enhances contrast discrimination and thus visual signal processing is initiated within the first synapses of the retina.

Acuity. Maximum acuity in the vertebrate retina would be achieved if each ganglion cell received information from a single cone at the receptive field centre. Indeed, this is the case in the central fovea (~ 0.6° visual field). Here, LW and MW cones are packed at densities approaching 200,000 cells/mm² and each cone synapses with a 'midget' (small dendritic field) ON- and OFF- bipolar cell. In turn these cells feed-forward to their corresponding 'midget' ganglion cell counterpart. This wiring pattern underpins the high spatial resolution in the central retina. Interestingly, there are very few SW-cones in the central fovea and all normal human subjects are tritanopic in this region. It appears that in the central retina chromatic sensitivity is sacrificed for acuity. In the peripheral retina, the cone density is lower and the bipolar cells in this region have larger dendritic fields and summate the input from multiple cones. This convergence results in reduced acuity in the peripheral retina.

Chromaticity. In order to initiate discrimination between different wavelengths of light, the responses of the different spectral cone classes are compared in an opponent manner. In the central retina, information originating from a single LW- or MW- cone can be relayed to a single midget ganglion cell.⁶ These cells are believed to generate LW and MW opponent responses suggesting that colour discrimination begins at the level of the retina. However, there is some controversy regarding how colour opponent responses are generated. The random wiring theory suggests that in the central retina (where ganglion cells receive input that originates from single cones) there should be strong opponency whereas in the peripheral retina (where information from several cones converge on to the receptive field centre of single ganglion cells) chromatic sensitivity would be reduced. However, it has been found that in the peripheral retina of macaques, LW versus MW cone opponency is no different to the centre.⁷ This would suggest the presence of selective cone wiring although there is no direct evidence to support this model. The SW cone pathway utilises a specialised bipolar cell feeding on to a ganglion cell that produces a blue ON/yellow OFF response.⁸

The Rod System

The cone system is active in photopic conditions however, at low light levels the retina relies on the rod photoreceptor cells. The outer seg-

ment region of these cells contains the photopigment rhodopsin. The phototransduction pathway in the rods is essentially the same as that in cones, whereby absorption of light results in membrane hyperpolarisation. The rods feed-forward to a single dedicated bipolar cell, the rod ON-bipolar cell. These cells depolarise in response to light via a similar mechanism to that found in the cone ON-bipolar cells. At this point similarities with the cone pathway cease. In mammals the rod pathway does not have a direct connection to the ganglion cells. The rod ON-bipolar cell contacts an AII-amacrine cell, which in turn contacts cone ON- and OFF- bipolar cells. The cone bipolar cells then follow their normal synaptic route to the ganglion cell layer. Thus the cellular pathway associated with the rod cell appears to piggy-back onto the cone pathway. Other pathways for transmission of the rod signal include rod-cone coupling and a possible direct input of rods to cone OFF-bipolar cells.

Sensitivity. Compared to the cone system, the rod system is more sensitive to light, permitting vision at dim light levels. This property originates at two levels, within the rod cell itself and also within the retinal neuronal network. In the rods, a single photon activates a rhodopsin molecule and can induce a detectable single quantal change in the membrane potential. In addition, the retinal neuronal network associated with the rod pathway is convergent, permitting summation of the light signal from many rods. The rod ON-bipolar cell receives inputs from 20-80 rods and several rod bipolar cells synapse onto an AII amacrine cell. This convergence reflects a system designed for sensitivity rather than acuity. No rods are present in the foveal region and hence peak scotopic sensitivity occurs 15-20 degrees off the visual axis.

The Melanopsin Ganglion Cell System

In contrast to the classical rod and cone visual photoreceptors the intrinsically photosensitive melanopsin ganglion cells reside in the ganglion cell layer, do not have a specialised cellular structure, and depolarise in response to light (Figure 1 inset). Melanopsin is a member of a novel opsin family and has recently been shown to form a fully functional photopigment.⁹ In the human retina the melanopsin ganglion cells number in the order of 2000 cells per retina. The native phototransduction cascade associated with the melanopsin ganglion cells remains unknown but it has been ascertained that the photocurrent is carried by Na⁺ and Ca²⁺ ions.^{3,5}

Irradiance Detection. The melanopsin ganglion cells perform a different function to the rod and cone photoreceptor cells. They signal changes in ambient lighting levels. Unlike the rods and cones, which adapt quickly to prolonged light stimuli, the melanopsin ganglion cells exhibit little adaptation. This irradiance information is used to drive non-image forming processes. For example the axons of the melanopsin ganglion cells project directly to the suprachiasmatic nucleus (the site of the central circadian pacemaker) and to the pretectum (which drives the pupillary light reflex).

Importantly light responses in these retino-recipient areas persist when all rod and cone cells are lost or ablated. It has been recently shown, both in rodents and primates that the melanopsin cells also project to brain regions associated with classical image forming vision.

Interaction with Rod and Cone Systems.

Recent evidence suggests that there is significant interplay between the classical photoreceptor cell systems and the melanopsin ganglion cells in the retina. The melanopsin ganglion cells receive input from the rod and cone cell pathways. Furthermore, the light responses of these cells are routed through gap-junctions to other inner retinal neurones.⁵ It has also been shown in humans that the novel irradiance system plays a role in the regulation of the cone pathway at the local retinal level.¹⁰

Conclusions

This review has attempted to describe the key functional features of the three channels of light detection in the retina. However, this is by no means a complete picture. For example, there are over 50 types of amacrine cells but details concerning their function are unclear. Increasing evidence suggests starburst amacrine cells may be directionally sensitive, but it is unclear if this is the case in primates. There is also a dearth of knowledge concerning the melanopsin ganglion cells with regards to their physiology and connectivity. The extent of interplay between the three light sensing channels also remains to be fully explored. It is amazing that after over a century of research into retinal neurobiology details of retinal circuitry are being amended and elucidated; remarkably new photopigments and even functional retinal pathways are still being identified.

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