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REVIEW

Blurring the Boundaries of Vision: Novel Functions of Intrinsically Photosensitive Retinal Ganglion Cells

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Abstract: Mammalian vision consists of the classic image-forming pathway involving rod and cone photoreceptors interacting through a neural network within the retina before sending signals to the brain, and a non image-forming pathway that uses a photosensitive cell employing an alternative and evolutionary ancient phototransduction system and a direct connection to various centers in the brain. Intrinsically photosensitive retinal ganglion cells (ipRGCs) contain the photopigment melanopsin, which is independently capable of photon detection while also receiving synaptic input from rod and cone photoreceptors via bipolar cells. These cells are the retinal sentry for subconscious visual processing that controls circadian photoentrainment and the pupillary light reflex. Classified as irradiance detectors, recent investigations have led to expanding roles for this specific cell type and its own neural pathways, some of which are blurring the boundaries between image-forming and non image-forming visual processes.

Keywords: melanopsin, intrinsically photosensitive retinal ganglion cells, ipRGCs, image-forming, non image-forming, rod, cone, photoreceptor, circadian, pupillary light reflex, light aversion, mood, development

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Introduction

In the mammalian eye, the image-forming pathway transmits highly sensitive color, temporal, and spatial light-dependent information from rod and cone photoreceptors through an intermediate retinal network of bipolar, amacrine, and horizontal cells which convey light-dependent responses via conventional retinal ganglion cells (RCGs) to the lateral geniculate nucleus (LGN). This pathway contributes to conscious vision. The second pathway, the non image-forming pathway, is an ancestral pathway that enabled species (including photosensitive microorganisms and invertebrates[1]) to sense light and irradiance levels as a key means for organism response and survival. Once image-forming vision evolved, many scientists believed that it replaced the ancestral visual system. However, mammals, including people and rodents, that had lost their image-forming visual system (rod and cone photoreceptor blind) still synchronized their circadian rhythm with the light cycle and exhibited a pupillary light reflex, raising the question of a third photoreceptor in the eye.[2–5] When melanopsin was shown to be an active photopigment expressed in a small subclass of RGCs, the search for this third photoreceptor ended and a new area of study opened up for enlightenment.[6–10]

Melanopsin containing intrinsically photosensitive retinal ganglion cells (ipRGCs) are unusual photoreceptors. They receive photic information from rods and cones via bipolar cells but contribute an additional photic dimension via melanopsin. Five classes, M1 through M5, of ipRGCs that differ by morphology, dendritic localization, melanopsin content, electrophysiological profiles, and projections, have been characterized to date in rodents, although only M1 and M2 classes have been identified in non-human primates.[11–17] Some distinguishing features of ipRGCs include their use of a $G_{q/11}$ and PLC/IP3 signaling pathway in contrast to the transducin G-protein and cyclic GMP pathway used by rod and cone opsins,[17–22] and their ability to show sustained firing under saturating and continuous light exposure.[13,23–25] This non image-forming pathway is classically thought to inform unconscious vision that photoentrains the circadian cycle, controls the pupil light reflex, and regulates activity levels (masking) and sleep, which has been extensively reviewed elsewhere.[1,17,26–30] This review will focus on recently illuminated functions and applications of this pathway, some of which blur the lines between conscious and subconscious vision, and the retinal neurons that act as gateways to this system, the ipRGC.

ipRGCs in the Image-Forming Visual Pathway

Recent experiments have blurred the distinction between image-forming and non image-forming visual pathways. The ability of rodless, coneless mice to perform pattern discrimination suggested that ipRGCs contribute to image-forming vision.[31] This was substantiated by anatomical findings in melanopsin reporter mouse lines that the M3/M4/M5 subclasses of ipRGCs project directly to the LGN,[31] a region dedicated to image-forming vision. A direct LGN projection encoding color and irradiance had previously been observed in non-human primates[16] but not in other species. Subsequent electrophysiological evidence estimated that 40% of LGN-cortical cells receive melanopsin-specific signals in rodents.[32] Closer examination identified the mouse M4 ipRGCs, which express low levels of melanopsin and were not previously well characterized, as a major input to the LGN.[15] These M4 cells were further identified as the well-known alpha ON ganglion cells capable of contrast detection.[15] Tiger salamander retinae also have ON ganglion cells that are intrinsically photosensitive, indicating evolutionary conservation.[33] Their importance in contrast detection was demonstrated when mice lacking melanopsin showed decreased contrast sensitivity which was further decreased in mice lacking the M2-M5 classes of ipRGCs.[34] These recent findings, that one of the ipRGC subclasses previously considered to contribute only to the non image-forming visual pathway, is actually a well-known component of the image-forming pathway and truly highlights that surprising and revolutionary knowledge is still being discovered.

Birth and Death of ipRGCs

The melanopsin phototransduction system is evolutionarily older than the rod and cone systems. Given its ancient origin and key role in light-dependent survival, it is not surprising that melanopsin is expressed prenatally and that ipRGCs are the first photoresponsive cells of the mammalian retina[35–40] and are capable

of detecting light embryonically.[41] More ipRGCs are initially generated than survive and programmed apoptosis sculpts the mature rodent retina to form a "photoreceptive net" which samples the entire retina with very little overlap.[35,39,42–45] The development of the mammalian retina proceeds such that rod and cone photoreceptors integrate with pre-established ipRGCs while forming their separate image-forming pathway. Separation of function is evident in retinae with improper pruning of ipRGCs. Disruption of Bax-mediated apoptosis in a mutant mouse line results in clusters of ipRGCs that are capable of photoentraining circadian rhythm via melanopsin but incapable of mediating photoentrainment using rod and cone signaling.[43] ipRGCs also play a key role in the light-dependent modeling of the visual system. During development, waves of coordinated activity sweep across the retina to direct wiring of the retina to central targets. Melanopsin-dependent photoreception increases the duration of these activity bursts; mice lacking melanopsin have decreased segregation of ipsi- and contralateral LGN projections.[46] The consequences of this small decrease (approximately 5%) in crossover remains unclear. For comparison, albinism causes severe increases in crossover in both rodents and people. Approximately 90% of retinal fibers project contralaterally (compared to the normal 55%), and is associated with nystagmus, strabismus, and amblyopia in people.[47]

While ipRGCs are the first photoreceptors to develop, they have a longer period of proliferation[48] and may be some of the last of the retinal neurons to die during the course of an organism's lifetime. Rod and cone photoreceptors are highly susceptible to degeneration, and diseases that affect rods and cones are the leading cause of blindness. RGCs also degenerate in diseases that cause increased pressure including glaucoma and ischemia, vascular disorders like diabetes, neurodegenerative diseases such as Alzheimer's disease and Parkinson's, as well as optic atrophy among others. In rodent models of many of these conditions and in human glaucoma, ipRGCs appear to be resistant[49–54] but not necessarily immune to degeneration.[55,56] This suggests protective factors may be expressed in ipRGCs compared to non-melanopsin RGCs. Identification of the mechanisms behind ipRGC survival may provide potential targets for disease treatment. Lastly, their long-term survival has made them a candidate for gene therapy. Not only are they more easily transfected by virus compared to cells in the outer retina, they are also likely to be healthier in a disease state.[57,58]

Novel Applications of Classic Functions of ipRGCs

The intrinsic circadian clock calculates an approximate 24 hour light/dark cycle.[59] Normal fluctuations in day length and phase delays from events like daylight savings require the ability to photoentrain this cycle,[60,61] a function of ipRGCs.[62,63] Axon collaterals within the retina allow intraretinal signaling between ipRGCs and dopamine-producing amacrine cells. Melanopsin is required for feedback control to maintain retinal dopamine levels high at night and low during the day.[64] This nighttime high level of dopamine increases gap junction coupling of rod-rod and rod-cone photoreceptors.[65,66] Coupling of rod photoreceptor both decreases noise and increases the effective receptive field, possibly allowing increased contrast detection to occur under scotopic or mesopic light conditions.[65,67] By directly regulating the levels of dopamine, ipRGCs influence detection of dim objects at night[68,69] but also are able to see.[70] Melanopsin is also required for enhanced cone photoreceptor responses during mid-day, with photoreceptor coupling to other retinal neurons the proposed mechanism for modulation of visual processing.[71] Together, these animal studies show how ipRGCs contribute to shaping responses of the image-forming pathways.

The pupillary light reflex is an important protective mechanism that regulates the amount of light reaching the retina. The circuit begins with light detection via rhodopsin, cone opsin, and melanopsin.[9,72,73] ipRGCs convey this irradiance information bilaterally,[62,63,74] specifically with M1 ipRGCs signaling the shell of the olivary pretectal nucleus.[48,75] The preganglionic parasympathetic neurons in the Edinger-Westphal nucleus and the ciliary ganglia complete the circuit controlling the sphincter muscles of the iris.[76] The pupillary light reflex consists of an initial fast constriction phase that is dominated by rod and cone photoreceptors, an escape phase characterized by some loss of constriction and a final sustained phase attributed to melanopsin.[25,77] Consequently, spectral sensitivity of the rod, cone, and ipRGC photopigments, as well as the different phases of the pupillary light reflex,

can be used to assess the functional state of the three photoreceptors in rodents, dogs, or humans.[78–81] Such differential diagnoses for rod or cone dystrophies and RGC damage are starting to emerge.[81–90]

It is often said that the eye is the window to the brain. This is particularly true with pupil responses that have been leveraged to assess the pupillary light reflex reflex loop, making it an ideal clinical diagnostic tool for concussion, stroke, and numerous neurological conditions.[85] Alterations in the ipsilateral and contralateral (consensual) responses can indicate sites of damage. Furthermore, unilateral stimulation of temporal retinal hemisphere results in greater constriction of the ipsilateral iris compared to consensual response in the contralateral iris.[91] The segregation of axons at the optic chiasm and subsequent innervation was suggested as a basis for this difference. An alternative mechanism identified in rodents, dogs, cats, and rabbits (but not in non-human primates) may also contribute to this difference as light-dependent constriction of an isolated iris muscle was recently shown to be melanopsin-dependent based on spectral sensitivity, immunohistochemistry, a melanopsin promoter-drive fluorescent tag, mRNA analyses, and loss of the effect in the absence of melanopsin.[92] This may be mediated by melanopsin-expressing cells in the iris or by projections from ipRGCs that synapse in the iris.[93] Both of these possibilities are intriguing as they represent identification of a novel cell type that expresses melanopsin or a novel projection of ipRGCs, respectively.

A Novel Nocifensive Role for ipRGCs

Nocifensive behaviors are protective behaviors associated with noxious stimuli. For bright light stimuli, these behaviors may include blinking, squinting, pupil constriction, and avoiding light. A direct role for melanopsin in light avoidance was shown in mouse pups. At a developmental stage in which only ipRGCs are photoreceptive, pups turn away from blue light, a response lacking in melanopsin-deficient mice.[94] This response was accompanied by ultrasonic vocalizations, which are used by rodents to communicate threats or danger, and activation of the posterior thalamus (implicated in migraine-related pain[95]) and the central amygdala (associated with nociception[96]). A direct role for ipRGCs in light aversion was also shown for adult mice. Innate light aversion, which is revealed by prior environmental and light exposure, is decreased in mice lacking ipRGCs but not rod and cone photoreceptors.[97,98]

The involvement of ipRGCs in clinical models of photoallodynia (ocular or headache pain initiated or modulated by normal light levels) is likely dependent on the etiology of photoallodynia. In a mouse model of dry eye damage caused by corneal application of a common preservative in ophthalmic solutions, light aversion is dependent on ipRGCs.[99] By contrast, ipRGCs are not required in a mouse model of nitroglycerin-induced migraine.[99] Other studies, however, have identified visually blind (lacking rod and cone photoreceptors) people that still experience photoallodynia, strongly suggesting that ipRGCs mediate this function in both migraine and non-migraine conditions.[95,100] Furthermore, supporting evidence from rodents shows that light directly or indirectly modulates migraine-related chemo- and mechano-sensitive dura neurons, which terminate in close apposition to ipRGC projections in a thalamic region mediating pain.[95] Light has also been shown to increase activation in the trigeminal nucleus devoted to pain perception,[101,102] although the photoreceptors required for this are unknown. The identification of a direct retinal-thalamic pulvinar tract may provide an anatomical basis for photoallodynia in people,[103] however an interesting twist came with recent findings showing that C1-C3 cervical nerves are also capable of evoking periorbital pain in migraine patients.[104] Together, these data highlight how little is known about the connection between light and pain.

Anxiety, Memory, and Mood Modulation by ipRGCs

The relationship between light and anxiety in rodents is well established.[105] Open and brightly lit spaces are typically characterized as dangerous environments, making a light/dark box exploration assay a good measure for anxiety and anxiolytic drugs.[106,107] Avoidance of light in a light/dark box is melanopsin-[108,109] and ipRGC-dependent[98] however anxiety from novel environments increases the level of light aversion,[98,110] indicating that ipRGCs mediate both innate and anxiety-induced light aversion. The aversive capacity of light is also observed in mice in pavlovian, associative conditioning to a noxious stimulus.[111,112] Normal and melanopsin-deficient mice showed enhanced learning in pavlovian fear conditioning, while mice lacking rod and cone

photoreceptors did not. This effect was not accompanied by increased anxiety,[112] suggesting an additional role for light in memory modulation (also, see below). Together, this suggests a complex role for light in anxiety and enhanced responses to fear memory.

A biological basis for the role of melanopsin in mood and depression was established when human mutations in melanopsin were linked to seasonal affective disorder (SAD).[113] SAD is associated with physiological, behavioral, and mood changes that are evident during winter months with a shorter photoperiod.[114] A link between light cycle, ipRGCs and mood was also shown in mice. A short photoperiod was associated with depressive behaviors including increased anhedonia in a sucrose preference test and increased hopelessness in a forced swim test, effects which were reversed with antidepressants.[115] The same shortened photoperiod also affected hippocampal-dependent spatial learning and memory, with a concurrent decrease in hippocampal-based synaptic plasticity,[115] the neural basis thought to underlie learning and memory.[116] Mice lacking M1 ipRGCs were protected from the effect of this shortened photoperiod on the forced swim test, and hippocampal memory and plasticity, suggesting that ipRGCs are required for regulation of mood/depressive state associated with circadian rhythm disturbances and learning deficits. Whether this role of ipRGCs is important for light-enhanced fear conditioning described above is unclear since ipRGCs were not tested and the memory task used was hippocampus-independent.

Conclusions

Light reaches essentially every corner of the brain to influences neural responses, either directly or indirectly. Specific neuroanatomical circuits define both the rod/cone photoreceptor dependent image-forming pathway and the ipRGC dependent non image-forming pathway. The latter pathway has projections to multiple regions with the potential to influence mood, pain, cognition, addiction, sleep, circadian rhythm, pupil responses, and even vision.[117] The identification of melanopsin as an active photopigment, and ipRGCs as unique photoreceptors has provided mechanistic explanations for the effect of light on many biological functions. The effect of these irradiation detectors on additional light-modulated functions remains to be elucidated.

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Wrote the first draft of the manuscript: AM. Contributed to the writing of the manuscript: AM. Made critical revisions and approved final version: AM. The author reviewed and approved of the final manuscript.

Competing Interests

Author discloses no potential conflicts of interest.

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As a requirement of publication the author has provided signed confirmation of compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the author was invited to submit this paper.

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