The melanopsin system

Phototransduction, projections, functions, and clinical implications

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The melanopsin system consists of retinal ganglion cells containing the photopigment melanospin, which are directly activated by light in the absence of inputs from the photoreceptors. These intrinsically photosensitive retinal ganglion cells (ipRGCs) detect environmental brightness; combine their direct, melanospin-triggered photoresponses with signals derived from rods and cones; and project to several targets in the diencephalon and midbrain. Via these projections, the melanospin system mediates several non-imaging-forming visual functions, including light entrainment of circadian rhythms and pupillary responses to light. The discovery of the melanopsin system explained the preservation of normal circadian rhythms, relative preservation of pupillary reflexes, and excessive light sensitivity in patients with visual loss due to disorders affecting the photoreceptors. The melanopsin-containing ipRGCs are relatively spared in inherited mitochondrial optic neuropathies, may be selectively affected in glaucoma, and may trigger photophobia in patients with migraine. Polymorphisms in the melanospin (opsin 4, Opn4) gene are associated with seasonal affective disorder. The functional organization of the melanopsin system and its implications in disease have been recently reviewed.[1-7]

ANATOMY AND PHYSIOLOGY OF THE MELANOPSIN SYSTEM

Intrinsically photosensitive retinal ganglion cells. Melanopsin (also called opsin 4, Opn4) is a photopigment that was first identified in frog skin and was thereafter detected in a small subpopulation of retinal ganglion cells in vertebrates.[8] The ipRGCs respond to light stimulation with depolarization in the absence of any synaptic input from rods and cones; hence their designation as intrinsically photosensitive.[1,9] The ipRGCs combine their direct, melanospin-triggered photoresponses with signals derived from rods and cones and project to several targets in the diencephalon and midbrain involved in circadian rhythms and pupil responses to light (figure) The ipRGCs constitute a small percentage of ganglion cells; in each human eye, up to 3,000 out of ~1.5 million retinal ganglion cells stain positively for melanopsin[10]; these cells are more concentrated in the parafoveal region and at the far end of the nasal hemiretina.[11]

Like all retinal ganglion cells, ipRGCs utilize the excitatory amino acid L-glutamate as their primary neurotransmitter; they also express pituitary adenylate cyclase-activating polypeptide (PACAP), which acts as a cotransmitter of glutamate in the retinohypothalamic pathway.[12] There are several subtypes of ipRGCs that differ in their dendritic distribution in the inner plexiform layer, melanopsin expression, physiologic responses to light, and connections.[3,13]

Melanopsin and phototransduction. Melanopsin-expressing ipRGCs have several features that distinguish them from the classic photoreceptors (table). Whereas rods and cones hyperpolarize in response to light, melanopsin-containing ipRGCs depolarize upon light stimulation. This reflects the differences between the signal transduction pathways triggered by activated melanopsin and those triggered by rhodopsin or cone opsins.[1]

Melanopsin is an opsin class of G-protein–coupled receptor that is expressed exclusively in ipRGCs in mammals.[8] The light response properties of melanopsin are distinct from those of the rods or cones opsins.[5,6] Melanopsin has a peak spectral sensitivity at ~480 nm, which lies in the blue/cyan range of the visible light. Like other opsins, melanopsin uses 11-cis retinaldehyde as a chromophore; light elicits photoisomerization of this chromophore resulting in conformational changes in the opsin receptor, which

GLOSSARY

DOA = dominant optic atrophy; **IGL** = intergeniculate leaflet; **ipRGC** = intrinsically photosensitive retinal ganglion cell; **LHON** = Leber hereditary optic neuropathy; **PACAP** = pituitary adenylate cyclase-activating polypeptide; **SCN** = suprachiasmatic nucleus; **SPZ** = subparaventricular zone; **VLPO** = ventrolateral preoptic nucleus.

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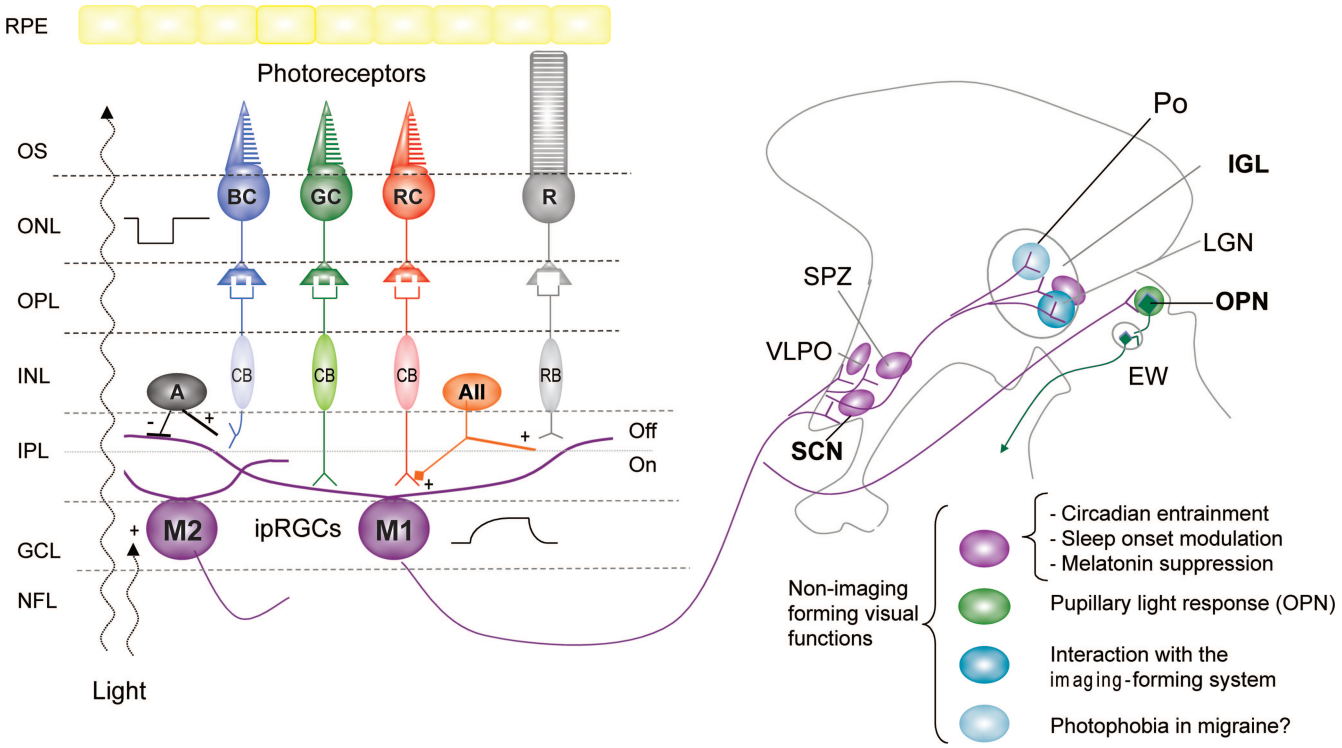
Figure Retinal and extrinsic connections of melanospin-containing ganglion cells



The melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs) have a giant soma and long, sparsely branching dendritic processes that extend either into the outer ("off ") sublayer of the inner plexiform layer (M1 cells) or the inner ("on") sublayer (M2 cells). These ipRGCs integrate their direct light responses with signals from rods and cones for non-imaging-forming functions. Rods provide excitatory inputs to ipRGCs sequentially via rod bipolar (RB), type II amacrine (AII), and cone bipolar (CB) cells. Red cones (RC, long wavelength, L-cones) and green cones (medium wavelength, M-cones) provide excitatory inputs to the proximal dendrites of ipRGCs through cone bipolar cells. In contrast, blue cones (BC, short wavelength, S-cones) trigger provide inputs presumably through cone bipolar cells and inhibitory amacrine (A) cells. The axons of ipRGCs exit the retina via the optic nerve and project to the suprachiasmatic nucleus (SCN), the subparaventricular zone (SPZ), the ventrolateral preoptic area (VLPO), and the intergeniculate leaflet (IGL) of the lateral geniculate nucleus (LGN), which are involved in circadian regulation, and to the olivary pretectal nucleus (OPN), which is a relay of the pupillary light reflex. Projections to the dorsal LGN provide an interface with the imaging-forming system; projections to dural-sensitive neurons in the posterior hypothalamus (Po) may contribute to light-induced exacerbation of migraine. EW = Edinger Westphal nucleus; GCL = ganglion cell layer; INL = inner nuclear layer; IPL = inner plexiform layer; NFL = nerve fiber layer; ONL = outer nuclear layer; OPL = outer plexiform layer; OS = outer segment; RPE = retinal pigment epithelium.

activates downstream signaling proteins.[1,5] The signal transduction cascade triggered by activated melanopsin is different from that triggered by metarhodopsin in rods and cones.[5] In photoreceptors, light-activated metarhodopsin is coupled to the G protein transducin, which activates phosphodiesterase E; this results in hydrolysis of 3′–5′ cyclic guanosine monophosphate and closure of cyclic nucleotide-gated cation channels, leading to hyperpolarization. In contrast, melanopsin is coupled to G_q, which activates phospholipase C-β and a cascade that involves diacylglycerol, protein kinase C, and inositol triphosphate (IP_3) as signal intermediates. This results in activation of transient receptor potential cation channels, eliciting influx of sodium and calcium and thus depolarization of ipRGCs.[1,6,14]

Functional properties and retinal connectivity of ipRGCs. The functional properties of melanopsin-containing ipRGCs and their signaling pathways (which operate over longer time frames) make them suited to function as irradiance detectors that integrate light information over long periods of illumination.[1] The melanopsin-containing ipRGCs have a giant soma and long, sparsely branching dendritic processes that extend either into the outer ("off") sublayer of the inner plexiform layer (M1 cells) or in the inner ("on") sublayer (M2 cells); at this level, they form an interconnected and bilayered dendritic meshwork.[5,9] The ipRGCs have a high threshold for activation, long response latency, and a prolonged duration of firing before return to baseline.[15] These properties distinguish the ipRGCs from the rod and cone photoreceptors, which are specialized for encoding fine spatial resolution and a transient, adaptable response required for image formation.

Interactions between the melanopsin and the photoreceptor systems. Experimental evidence indicates that ipRGCs are the principal cells that integrate the light responses from rod, cone, and melanopsin systems for non-imaging-forming functions.[5] There are reciprocal

Table Differential features between the classical and the melanopsin photoreceptive pathways

Pathway	Classical (imaging-forming)	Melanopsin (non-imaging-forming)
Photoreceptor cell	Rods and cones	Intrinsic photosensitive retinal ganglion cells
Photopigment	Rhodopsin, cone opsins	Melanopsin
Light sensitivity	All visible wavelengths	Broad band, most sensitive to blue wavelength
Response to light	Hyperpolarization	Depolarization
Receptive fields	Very small	Very large (photosensitive net)
Properties	Fine spatial resolution	Temporal integration of ambient light (irradiance)
Main target of ganglion cells	LGN	Suprachiasmatic nucleus
	Superior colliculus	Subparaventricular zone
	Olivary pretectal nucleus	Ventrolateral preoptic area
		Intrageniculate leaflet of the LGN
		Olivary pretectal nucleus
Function	Image formation	Entrainment of circadian clock
	Pupillary light reflex (early and transient response)	Light-induced sleep regulation and inhibition of melanotonin secretion
		Pupillary light reflex (sustained response)
Involvement in disease	Affected in rod-cone dystrophies	Affected in SAD
	Affected in mitochondrial optic neuropathy	Affected in glaucoma
		Relatively spared in mitochondrial optic neuropathy

Abbreviations: LGN = lateral geniculate nucleus; SAD = seasonal affective disorder.

interactions between the melanopsin (non-imaging-forming) and the rod/cone (imaging-forming) systems at several levels. Like other retinal ganglion cells, the ipRGCs transduce light responses initiated by rods and cones[5,9] (figure). Rods as well as red (long wavelength, L) and green (medium wavelength, M) cones trigger an "on" response in ipRGCs; blue (short wavelength, S) cones trigger an "off" response.[1] Recordings from primate ipRGCs show distinct rod, cone, and melanopsin-initiated responses in ipRGCs.[15] In dim light conditions, rod signals trigger sustained action potentials in ipRGCs; as the light intensity increases to levels encountered during daytime, signals from L- and M-cones cause a transient depolarization of the ipRGCs at the onset and offset of light. The direct, melanopsin-triggered photoresponses begin after a few milliseconds of cone-initiated response and are sustained for the duration of illumination.[15]

The ipRGCs also interact with dopaminergic amacrine cells in the retina, which are involved in mechanisms of light adaptation. Both M1 ipRGCs and dopaminergic amacrine cells receive inputs from ON bipolar cells[16]; the ipRGCs provide excitatory drive to the dopaminergic neurons[17] and dopamine increases melanopsin expression in ipRGCs.[18] However, studies in melanospin knockout (Opn4 −/−) mice indicate that melanopsin is neither necessary nor sufficient for light regulation of retinal dopamine.[19]

Extrinsic connections of the melanopsin-containing ipRGCs. The axons of ipRGCs exit the retina via the optic nerve and project to distinct regions of the brain (figure). These projections provide the substrate for a variety of irradiance-driven, non-imaging-forming responses triggered by light, including entraining of circadian rhythms and the pupillary light reflex.[2] The primary targets of melanopsin-containing ipRGCs are the suprachiasmatic nucleus (SCN), the intergeniculate leaflet (IGL) of the lateral geniculate nucleus, and the olivary pretectal nucleus. Other important targets include the ventral subparaventricular zone (SPZ) and the ventrolateral preoptic nucleus (VLPO).[2,20-22] Via their projection to the SCN, IGL, SPZ, and VPO, melanopsin cells mediate light entrainment of circadian rhythms; via connections to the olivary pretectal nucleus, they trigger the pupillary light reflex. The ipRGCs also project to areas involved in imaging-forming functions, such as the dorsal lateral geniculate nucleus and the superior colliculus. Other targets include the lateral habenula, which is a relay site between limbic and striatal areas, and the amygdala. Although subsets of melanopsin-containing ipRGCs may preferentially innervate different targets, the majority of individual ipRGCs send axon collaterals to multiple targets.[2,20-22]

FUNCTIONS OF THE MELANOPSIN SYSTEM

Light entrainment of the circadian rhythms, sleep, and melatonin secretion. The melanopsin-containing ipRGCs and their brain targets constitute a retinal irradiance system that drives or contributes to a variety of non-imaging-forming light-induced responses, including photoentrainment of circadian rhythms, suppression of melatonin secretion, modulation of sleep by light, and pupillary light reflex.[2] Studies in melanopsin knockout (Opn4−/−) mice support the critical role of this system in all these functions.[1,5,23]

Most melanopsin-containing ipRGCs project to the SCN, which is the circadian pacemaker, via the retinohypothalamic tract.[2,12] This pathway conveys photic information to the SCN, synchronizing the circadian pacemaker to the 24-hour solar cycle. Melanospin-containing projections to other targets connected with the SCN, including the SPZ, IGL, and VLPO, could provide multiple additional parallel pathways for light influences on circadian rhythms.[2] The ventral SPZ relays SCN influences on other hypothalamic targets[24] and, like the SCN, receives inputs from the IGL, which conveys information to the circadian clock via the geniculohypothalamic tract.[25] Both the SCN and SPZ

project to the VLPO, which contains sleep-inducing neurons that inhibit the brainstem monoaminergic and cholinergic arousal systems.[26] The SCN sends inhibitory projection to the paraventricular nucleus, which controls melatonin secretion via the sympathetic system. Thus, the melanopsin projections to the SCN, SPZ, and VLPO participate in light entrainment of circadian rhythms, sleep induction, locomotor activity, and suppression of melatonin secretion.[4] Studies on Opn4−/− mice suggest that melanopsin is also involved in the buildup of sleep pressure during wakefulness, which is a fundamental aspect of sleep homeostasis.[27]

Pupillary light reflex. Melanopsin-containing ipRGCs provide a major contribution to the afferent limb of the pupillary light reflex.[28] These neurons send a direct projection to the olivary pretectal nucleus of the midbrain; this nucleus projects to the Edinger-Westphal nucleus, which sends efferents to the ciliary ganglion. Melanopsin-containing ipRGCs drive the pupillary light reflex in the absence of input from photoreceptors, as shown in *Opn4* null mice.[29] The discovery that melanopsin-containing ipRGCs mediate the pupillary light reflex has provided new insights into the pupillary response to light.[1,28] Under photopic conditions, a red light stimulus produces a pupil constriction mediated predominantly by cone inputs via trans-synaptic activation of melanopsin-expressing ganglion cells; a blue light stimulus produces a steady-state pupil constriction mediated primarily by direct intrinsic photoactivation of these cells. Preliminary studies in humans also indicate that cones primarily drive the transient phase of the pupil light reflex, whereas melanopsin-expressing ganglion cells directly activated by light mediate sustained pupil constriction.[1,28]

Interactions with the imaging-forming visual system. In addition to its primary role in non-imaging-forming functions, the melanopsin system may directly transmit ambient light intensity information to the imaging-forming visual system. The ipRGCs send projections to the dorsal LGN, which is the primary relay for imaging-forming signals from the other retinal ganglion cells.[15] The ipRGCs also send inputs to the superior colliculus, which is involved in visually triggered orientation and projects to the pulvinar a major relay of the posterior parietal visual attention system.[3] In normal individuals, these ipRGC projections could provide brightness information for imaging-forming vision. Via these projections, some blind patients with substantial loss of rod/cone photoreceptors may have rudimentary visual perception.[5]

CLINICAL CORRELATIONS

Inherited optic neuropathies. Inherited optic neuropathies due to mitochondrial dysfunction, including Leber hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA), initially affect the parvocellular retinal ganglion cells that project via the papillomacular bundle; this causes loss of visual acuity, cecocentral scotoma, impaired color vision, and optic atrophy. However, patients with LHON and DOA have relatively preserved pupillary light reaction, photoentrainment of circadian rhythms, and light suppression of melatonin secretion.[7,11,30,31] Recent studies show that the basis for this dissociation is the relative preservation of melanopsin-containing ipRGCs in these mitochondrial optic neuropathies.[11] These cells are lost in patients with LHON and DOA at a much slower rate compared with the other ganglion cells, as demonstrated in postmortem retinal and optic nerve specimens.[11] The mechanisms underlying the relative resistance of melanopsin-containing ipRGCs to energy failure and oxidative stress in these mitochondrial disorders are unknown. Potential contributory factors include the abundant expression of cytochrome oxidase in mitochondria in these cells, the neuroprotective effect of PACAP, and the effects of the signal cascade triggered by melanopsin, which absorbs short wavelength light.[11]

Glaucoma optic neuropathy. Glaucoma is the most common optic neuropathy. Classically, the pattern of loss of retinal ganglion cells results first in selective involvement of nerve fibers in the arcuate bundle. There is evidence that, unlike the case of hereditary optic neuropathies, the melanopsin-expressing ipRGCs are as severely affected as other ganglion cells in glaucoma. Furthermore, preliminary data in humans suggested abnormal circadian rhythm of melatonin secretion and of light-induced melatonin suppression in glaucoma patients, which is consistent with experimental models.[32,33] The pupillary light reflex is also compromised in glaucoma patients.[34]

Migraine. Light exacerbates migraine headaches and several migraineurs have aversion to light (photophobia). The preservation of these symptoms in blind individuals with light perception implies the potential involvement of the melanopsin system.[1,7,35] Noseda et al.,[35] using single-unit recording and neural tract tracing in the rat, identified dura-sensitive neurons that were modulated by light and projected extensively to the somatosensory, visual, and associative cortices. These dura/light-sensitive neurons were apposed by axons from melanopsin-containing ipRGCs.[35] These findings suggest a role of the melanopsin system in mediating migraine-related photophobia.

Seasonal affective disorder. Seasonal affective disorder is a common mood disorder that is characterized by the annual recurrence of depression in fall and winter, with remission in the spring and summer

months. There is evidence for abnormalities of hormonal circadian rhythms in this disorder. Genetic studies showed that a missense variant (Pro10Leu) of the *OPN4* gene increases the risk of developing seasonal affective disorder, supporting a role of the melanopsin system in this condition.[36]

PERSPECTIVE The discovery of the melanopsin system expands our understanding of the physiology and pathophysiology of vision. The spectral sensitivity, responsiveness, and selective vulnerability of the melanopsin-containing retinal ganglion cells have implications in the differential diagnosis of conditions associated with visual loss. For example, the use of chromatic light stimuli to elicit transient or sustained pupil light reflexes may allow differentiation between disorders affecting photoreceptors and those affecting retinal ganglion cells.[1,28] The insights into the melanopsin system can also be applied to the management of several ophthalmologic, neurologic, and psychiatric disorders. For example, exposure to visible light in the blue range may improve circadian regulation of sleep in elderly patients with cataracts, whereas selective protection against this wavelength may reduce photophobia in patients with migraine, as discussed in a recent review.[5]

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