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Melanopsin's Newly Identified Functions Related to Behavioral Light Adaptation

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Abstract: *The ability of behavior and physiology to adjust to variations in ambient light brightness is essential to survival. These adaptations include the circadian clock's alignment of physiology and behavior to the day-night cycle and the modulation of neuroendocrine activity by light. These non-image-forming (NIF) responses are dependent on ocular light receipt but can work independently of rod and cone photoreceptors, indicating the involvement of novel photoreceptors in the eye. A fascinating entrance point to understanding how mammals adjust to the light environment has been made possible by the discovery of melanopsin in intrinsically photosensitive retinal ganglion cells (ipRGCs) and genetic evidence for its significant role in major NIF responses. Here, we examine the most recent developments in our knowledge of the ipRGCs and melanopsin's newly emerging roles. These discoveries now open up new perspectives on how ambient light affects alertness, sleep, dependent physiologies, potential pharmacological intervention, and lifestyle changes to enhance quality of life.*

Keywords: Melanopsin (OPN4), retinal ganglion cells (RGC), intrinsically photosensitive retinal ganglion cell (ipRGC), retina, non-image forming (NIF) photoresponse, the circadian clock, and opsin

I. INTRODUCTION

Rod, cone, and ipRGC photoreceptors are the three types.

The majority of the photoreceptor cells in the mammalian retina are rods and cones in the outer retina. They have extremely high spatial and temporal sensitivity to light, which is the foundation of image-forming (IF) vision. Loss of IF vision results from severe rod/cone dysfunction or rod/cone cell death. The ability of many humans and animal models with significant rod/cone loss to support some NIF activities, however, has long been known [1-3] (Box 1).

In subjects who have lost both eyes are eliminated [4]. Both normal and blind participants with significant rod/cone loss exhibit peak spectral sensitivity of several of these NIF responses in the 460–500 nm range in both people and animal models [5–11].indicating that alternate photoreceptors are crucial for NIF responses. The identification of melanopsin in a small subset of inner retinal retinal ganglion cells (RGCs) [12,13],As a result of these cells' inherent photosensitivity [14,15] and genetic evidence that rod, cone, and melanopsin are responsible for all mammalian ocular photoresponses [8,16–19], it is now possible to fully comprehend how the inner and outer retinal photoreceptors work together to adjust to the ambient light environment.Recent research has shown a formal connection between melanopsin function and a number of physiological and behavioral responses to light in different mammals. These investigations will aid scientists in comprehending the effects of modern medical procedures, pharmaceutical treatment, and efficient lighting tactics on people's quality of life.

Melanopsin, an opsin family of G-protein-coupled receptor (GPCR) that mediates the adaptation of skin pigmentation to ambient light level, was first identified in the photosensitive skin melanophores of Xenopus laevis, hence the name [20]. The retinas of various animals' were later found to contain melanopsin (reviewed in [21]).Melanopsin protein, also known as OPN4, is only expressed in a limited portion of intrinsically photosensitive RGCs (ipRGCs) in the inner retina in primates and rats (Figure 1). The light response characteristics of melanopsin and ipRGCs are different from those of the photopigments and photoreceptors of the outer retina, according to research conducted mostly in mice.

We shall refer to the cellular duties of ipRGCs and the molecular functions of melanopsin as "the melanopsin system" to keep things simple.ipRGCs' cellular architectures. Here, we discuss how rod/cone and melanopsin function are combined to determine NIF responses, as well as our current understanding of the molecular function of melanopsin,

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the cellular structure of ipRGCs, and these concepts. We finish up by talking about how these reactions might affect human health and sickness.

Glossary

Suprachiasmatic nucleus (SCN), circadian clock, and photoentrainment:

The circadian clock, an endogenous oscillator, regulates a wide range of physiological and behavioral changes with daily regularity. The SCN of the hypothalamus houses the primary circadian clock that controls behavioral rhythms. The intrinsic period of the circadian clock is not exactly 24 hours, and variations in day duration occur naturally over the course of the solar year due to the planet's axial tilt. Thus, light is the primary factor that influences the clock's phase each day. Circadian photoentrainment is the word used to describe how the intrinsic clock adjusts (entrains) to the phase or timing of environmental light.

Photoreceptors: are cells that detect light by expressing photopigments, which then activate signaling pathways (phototransduction) to control light-dependent physiological processes like vision, circadian rhythm regulation, seasonal reproduction, and body color changes. Rods, cones, and ipRGCs are the three different types of photoreceptors found in the retina of vertebrates. A photopigment known as 11-cis retinal, a light-absorbing molecule (chromophore) based on vitamin A, is found in every vertebrate photoreceptor (Figure 2).

Retinal ganglion cells (RGCs): serve as output neurons that transmit visual information to the central nervous system. They are located in the innermost layer of the retina, known as the GCL (Figure 1a).

Although this number varies between species, morphological characteristics can be used to classify at least 10-15 different types of RGCs [117].

Intrinsically photosensitive retinal ganglion cells (mRGCs/ipRGCs) with melanopsin: Melanopsin, commonly known as OPN4, is a protein expressed by a limited group of inherently photoreceptive mammalian RGCs. As a result, they are commonly known as ipRGCs or mRGCs.

Circadian clock, photoentrainment, and suprachiasmatic nucleus (SCN):

An endogenous oscillator called the circadian clock regularly controls a variety of physiological and behavioral processes. The principal circadian clock responsible for regulating behavioral cycles is located in the hypothalamic SCN. Because of how tilted the earth is, the intrinsic period of the circadian clock is not exactly 24 hours, and changes in day length happen in a solar year. The fundamental component affecting the clock's phase each day is hence light. The term "circadian photoentrainment" is used to explain how the intrinsic clock adjusts (entrains) to the phase or timing of external light.

RGCs, or retinal ganglion cells: act as output neurons that send visual information to the brain. They are situated in the GCL, the retina's deepest layer (Figure 1a).

Although the exact number varies between species, at least 10 to 15 different types of RGCs can be distinguished using morphological traits [117].

Melanopsin-containing intrinsically photosensitive retinal ganglion cells (mRGCs/ipRGCs): Melanopsin, also referred to as OPN4, is a protein that is only expressed by a small subset of mammalian RGCs that are innately photoreceptive. They are therefore frequently referred to as ipRGCs or mRGCs

Photoreceptors: are cells that detect light by expressing photopigments. These signaling pathways are subsequently activated (phototransduction) to regulate physiological activities that are dependent on light, such as vision, circadian rhythm regulation, seasonal reproduction, and changes in body color. Vertebrate retinas have three main kinds of photoreceptors: rods, cones, and ipRGCs. Every photoreceptor in a vertebrate contains 11-cis retinal, a photopigment that is a light-absorbing molecule (chromophore) derived from vitamin A (Figure 2).

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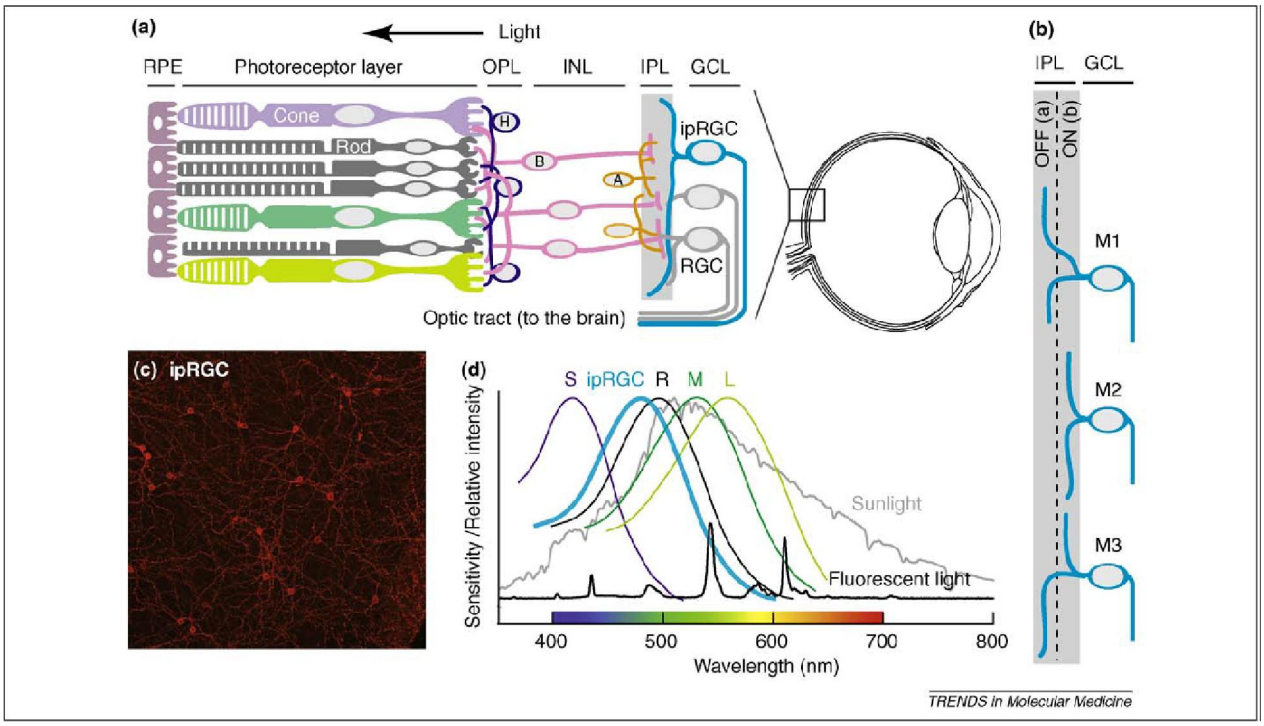

Figure 1: **shows the spectral characteristics of RGCs expressed by melanopsin.(see [43]).**

Schematic representation of the mammalian retina, highlighting the many cell types and connectivity patterns. The main photoreceptors supporting IF vision are the rod and cone photoreceptors that are tightly clustered in the outer retina. Before reaching the RGCs of the inner retina, light-activated signals coming from the rod/cone cells are processed in the horizontal (H), bipolar (B), and amacrine cells (A). A small proportion of RGCs (ipRGCs) that express melanopsin are intrinsically photosensitive. Like other RGCs, the ipRGCs also pick up signals from the outer retina's rod and cone photoreceptors. RPE stands for retinal pigment epithelium. OPL stands for outer plexiform layer. INL is for inner nuclear layer. IPL stands for inner plexiform layer.

(Rodent melanopsin-expressing RGCs display a variety of cellular architectures [68,116]. The sublamina a (OFF sublamina) in the IPL's outer half is where M1 subtype dendrites arborize most frequently. Unlike the M3 subtype, which stratifies in both sublaminae a and b, dendrites of the M2 subtype stratify in the inner sublamina of the IPL, the sublamina b (ON sublamina). The ON sublamina (also known as the ON sublamina) and the OFF sublamina, respectively, are home to the terminals of ON and OFF bipolar cells, respectively.The M1 cell type in the OFF sublamina, however, has peculiar ectopic synaptic connections with the ON bipolar cells [70].

Anti-melanopsin antibody-stained flat mount of a mouse retina. In contrast to the primate retina, which has a substantial ipRGC deficiency in the fovea, the distribution of melanopsin-staining cells in the mouse retina is essentially uniform [57]. RGCs that express melanopsin contain sparsely branched dendrites that can reach lengths of several hundred microns. In the retinas of primates and mice, these RGCs' dendritic fields have an average diameter of 0.5 mm [57] and 0.3 mm [65], respectively. Thus, despite only 1-2% of RGCs expressing melanopsin, these RGCs nonetheless produce a diffuse photosensitive web that almost covers the entire retina. Contrary to rods and cones, whose photopigment expression is limited to the outer segments, melanopsin immunoreactivity is present throughout the dendrites, soma, and axons.

The spectrum composition of indoor fluorescent lighting and sunlight, as well as the spectral sensitivity of rod, cone, andipRGCs. Human rods (R), S cones, M cones, and L cones have maximum light sensitivity ranges of 500 nm, 420 nm, 530 nm, and 560 nm, respectively. At 480 nm, the ipRGCs show their highest sensitivity. Using an EPP2000 UV-VIS spectrometer and SpectraWiz software (StellarNet Inc.), the emission spectra of common fluorescent lamps (black line) used for indoor lighting and sunlight (gray line; two hours on April 2010, shortly after daybreak in San Diego) were measured and examined.

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Box 1. Light adaptation or NIF visual photoresponse

The eye mediates a number of light-dependent reflexes, physiologies, and behaviors in addition to performing the IF function. Among these NIF responses are:

Circadian photoentrainment: In the majority of animals, an inherent circadian oscillator aids in temporally orchestrating the organisms' behavior and physiology to the right time of day. The inherent periodicity of the circadian clock is nearly, but not exactly, 24 hours in many animals, including mice and humans.The circadian clock must be regularly synchronized with the ambient light:dark environment in order to function as a reliable timekeeper. The circadian oscillator is strongly stimulated by light to become synchronized with the natural cycle of light and darkness.

The circadian clock's threshold sensitivity is several seconds or minutes, orders of magnitude less sensitive than IF eyesight. In the face of sporadic light noise in nature, such as lightening, such a demand for the integration of light information across longer periods aids in the maintenance of a reliable circadian clock. Mice lacking melanopsin (Opn4/ mice) have been shown to have reduced circadian clock light input [16,17].

Pupillary light reflex (PLR): The sudden narrowing of the pupil as a result of an increase in the amount of light reaching the retina. Constricting the pupil of the other eye after shining a light in one causes a consensual response. Melanopsin supports continuous pupil constriction in conditions of intense light [18].

Light suppression of activity: is the abrupt drop in activity that nocturnal animals experience during their active period in reaction to light.

When exposed to sustained illumination, mice missing melanopsin exhibit acute activity reduction at the onset of the light pulse [106].

Alertness : Humans and other diurnal species exhibit increased alertness and mood in bright light [10].

Acute suppression of pineal melatonin: In animals, the pineal gland is the principal source of circulating melatonin. The production and blood levels of melatonin peak at night in both nocturnal and diurnal species. Pineal melatonin production and secretion can be severely suppressed by light exposure for a few minutes to several hours. When retinal degeneration (rd) mice are used, their peak spectral sensitivity is intact [108] and different from that of rod/cone photoreceptors [107]. Mice that are homozygous for the rd allele lose their ability to see because of a primary degeneration of their rods and a subsequent loss of their cones, but they still have RGCs that carry melanopsin. The pineal melatonin production pathway is not light-suppressed in mice lacking both the rod/cone and melanopsin systems [19].

Light modulation of sleep: Sleep is modulated by light in nocturnal species, while diurnal animals experience a suppression of sleep. In Opn4-/- mice, a light pulse during the dark phase is unable to cause them to fall asleep.

Melanopsin only participates in the direct effects of light during the night. Furthermore, under a 12 hr: 12 hr light: dark schedule, Opn4-/- mice sleep around one hour less than wild-type mice [109-111].

Migraine exacerbation by light: Light makes migraines worse, and this effect is present in blind people who can perceive light but not in patients who cannot. The neurological mechanism for the light exacerbation response is provided by the direct projections of ipRGCs to the thalamic area, which is associated with migraine pain [43].

Allodynia to light or photophobia: A number of people, including some blind persons, exhibit allodynia to light or photophobia. Blind individuals with intact photophobia suggest that the melanopsin system may be involved. Additionally, before the rod/cone system is fully developed, immature rat pups (less than 10 days old) exhibit photophobia [112]. At this age [67], a fully functional melanopsin system most likely mediates such photophobia.

Photopigment melanopsin

Melanopsin photopigment exhibits maximal spectral sensitivity at 480 nm, which is different from that of traditional rod/cone opsins [22] and falls in the visible light spectrum's blue/cyan range (Figure 1d). The peak sensitivity aligns with the photosensitivity of a number of NIF responses in animals or people under prolonged exposure to light in the wild when rods and cones have saturated or acclimated, indicating that melanopsin plays a significant role in a number of NIF responses.

Melanopsin, like other photopigments in the opsin class, uses 11-cis retinaldehyde as a chromophore (light-sensing ligand; Figure 2). When activated by light, this chromophore photoisomerizes to all-trans retinal, which changes the protein's conformation and triggers the activation of downstream signaling proteins. At physiological temperatures, the

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traditional vertebrate rhodopsin photopigment is unstable in its light-activated or metastate. Contrarily, Drosophila rhodopsin transitions into a very stable metastate after being activated by blue light, continuing to activate downstream signaling proteins. Additionally, the metastate returns to the blue-sensitive basal state upon stimulation with long wavelength orange light (reviewed in [23]).Similar bistability is found in urified amphioxus melanopsin [24]. Although there is still a dearth of clear experimental evidence using isolated mammalian melanopsin, several observations point to melanopsin's bistable nature [25,26].The melanopsin photocurrent persists for more than 10 minutes after the lights go out in Xenopus oocytes that are expressing mouse melanopsin. However, 2 minutes after the lights go out, the photocurrent returns to baseline due to the coexpression of arrestin [27]. Arrestin de-sensitizes activated GPCRs [28] and the prolonged depolarization of Drosophila photoreceptor cells lacking arrestin is similar to the extended photocurrent of melanopsin in the absence of arrestin[29].The metastate melanopsin may therefore be stable. A long wavelength light pulse may cause the metastate mammalian melanopsin to return to the basal-blue absorption state if it behaves like purified amphioxus melanopsin or Drosophila rhodopsin. Melanopsin-driven photoresponses are potentiated by preceding irradiation with red-shifted light, providing evidence in favor of this concept [26,30,31].Despite these findings, direct evidence of melanopsin bistability in the intact ipRGCs and its implications in a setting with natural light have not yet been investigated. How variations in ambient light's spectral quality modify melanopsin signaling will depend on our knowledge of the metastate melanopsin.

The melanopsin's retinal source

Melanopsin's photochemical and spectral characteristics have clear effects on human health and way of life. Unknown processes lead to the regeneration of melanopsin pigment after photoactivation and the original source of 11-cis retinal. Understanding retinoid usage by melanopsin is crucial because deficiencies in retinoid metabolism are linked to a variety of human illnesses, and because components of the retinoid metabolism pathway have also been the subject of various treatment strategies [32]. The retinal pigment epithelium (RPE) in the retina is a location for the regeneration of cis-retinoid from all-trans retinoid and also acts as a large local storage of 11-cis retinal (Figure 2). Functions of the outer retina's rod and cone photoreceptors are supported by 11-cis retinal from the RPE [32]. There is some evidence that the RPE aids in the function of the melanopsin, but the exact mechanism by which it does so is the subject of intense controversy. Rpe65-/- or Lrat-/- mice produce minimal cis-retinoid,[33,34] which is mostly utilized by the outer retina rod photoreceptors and leaves little retinoid for melanopsin function. Rpe65-/- and Lrat-/- mice exhibit diminished melanopsin photosensitivity, diminished pupillary light response (PLR), and diminished circadian clock sensitivity as a result. The genetic ablation of the outer retina photoreceptors or the exogenous replacement of cis retinal can both increase these NIF responses [35–37]. These investigations have unequivocally shown that interference with RPE survival or function may also influence melanopsin activity. Therefore, it is likely that the substantial loss of PLR and poor sleep quality in visually impaired patients who carry hypomorphic or null alleles of Rpe65 [38-40] are caused by decreased melanopsin function. Because of their residual photosensitivity, Rpe65/ and Lrat/ mice may use melanopsin or the ipRGCs to recycle some all-trans retinal photoproduct into 11-cis retinal [37]. Melanopsin can photoisomerize all-trans retinal to 11-cis retinal and re-generate an active photopigment, according to indirect evidence [27]. However, it has been discovered that only 11-cis retinal is in a combination with pure melanopsin from mouse retinas [22]. This suggests that either the melanopsin-all-trans retinal complex is unstable and the all-trans retinal dissociates after initial light activation, resulting in the photobleaching of melanopsin, or the all-trans retinal Photoproduct remains attached to the opsin and is isomerized spontaneously to 11-cis retinal. Mammalian ipRGCs provide evidence for both photoisomerization and photobleaching mechanisms. In support of photoisomerization within ipRGCs, numerous labs have demonstrated that ipRGCs can be repeatedly photoactivated without exogenous retinal [14,15]. Others have noticed, however, that after repeatedly photostimulating ipRGCs, photoresponses or photobleaching can be reduced by up to 70% [41]. It is acceptable to say that while some melanopsin can photoisomerize the all-trans retinal and create functional photopigments, some melanopsin is bleached upon illumination and regenerated in the intact retina from cell autonomous or extracellular sources. Unknown processes and molecules control the steady-state concentrations of melanopsin photopigments. Melanopsin's partial bleaching and dependence on the RPE for at least some of its retinal supply present some intriguing clinical questions. Attenuating the visual cycle in RPE cells or limiting the availability of retinoid to the photoreceptors are two promising therapeutic

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strategies for halting or delaying the onset of various forms of blindness [42]. One such inhibitor of the visual cycle, all-trans-retinylamine, attenuates rod/cone function by rapidly reducing the amount of 11-cis retinal that is available while mostly preserving the melanopsin system [37]. However, the impact of long-term use of these medications on the melanopsin system is not yet known and needs to be carefully evaluated. It is possible to create melanopsin inhibitors, which can outperform cis retinal and lock melanopsin in an inactive state, if melanopsin is photobleached under extended illumination. Such inhibitors may cause "pharmacological darkness" and may lessen the melanopsin-dependent worsening of migraine pain in both normal and blind people (see [43]).

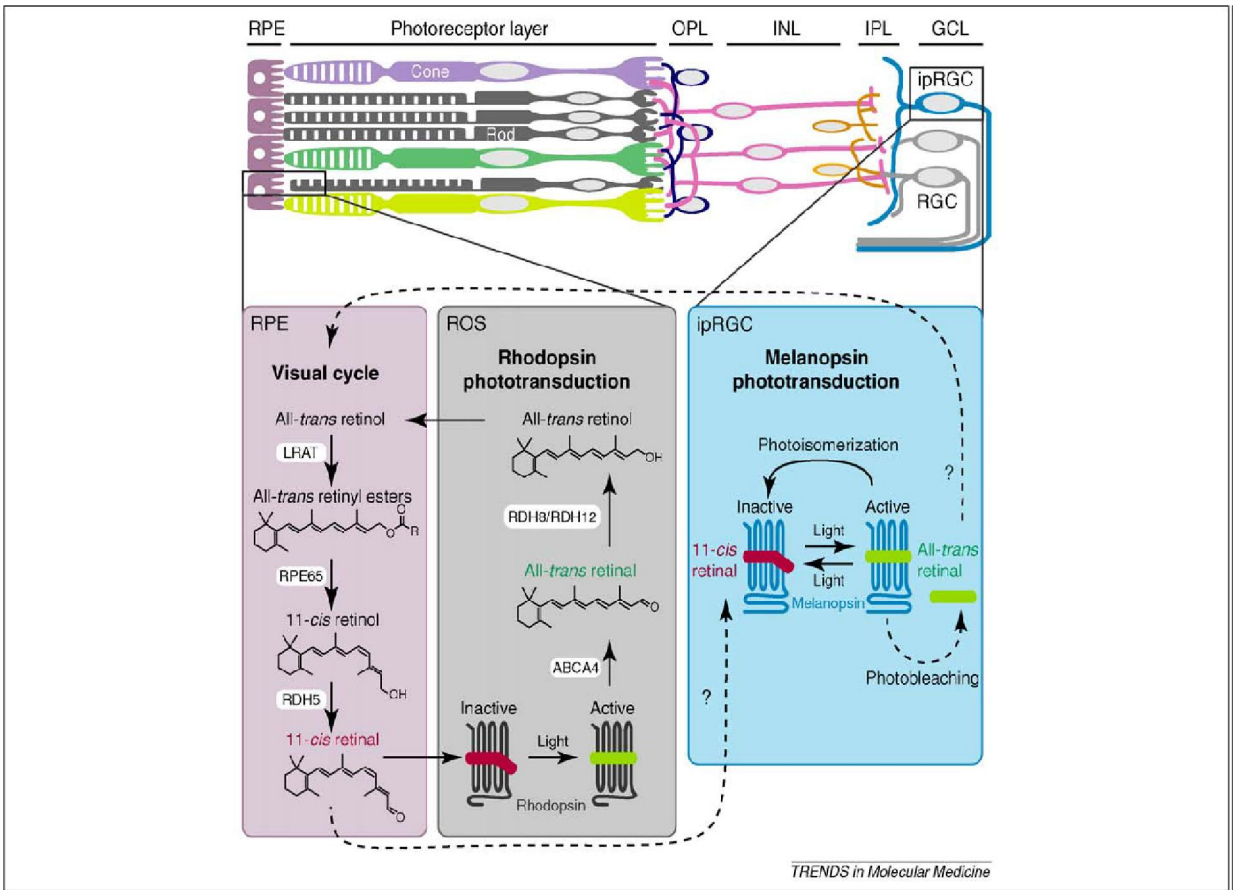

Figure 2: shows the phototransduction and visual cycle in the retina of vertebrates.severalhuman illnesses, such as blindness.

Rhodopsin's 11-cis retinal chromophore is converted to all-trans retinal in the rod outer segment (ROS) by light. Rhodopsin releases all-trans retinal, which then goes through a complex, multi-step enzymatic process (the visual cycle) to regenerate 11-cis retinal. Retinal dehydrogenases 8 (RDH8) and 12 first convert all-trans retinal to all-trans retinol. LRAT (lecithin retinol acyltransferase) converts all-trans retinol to all-trans retinyl esters in the RPE. All-trans retinyl esters are converted by RPE65

(Retinal pigment epithelium-specific protein 65 kDa) to 11-cis retinol, which is then oxidized by RDH5 to 11-cis retinal. In order to replenish the rhodopsin photopigment, 11-cis retinal travels back to the ROS where it attaches to opsin. Melanopsin and 11-cis retinal are discovered in complex in ipRGCs [22].It is presently unknown where this chromophore comes from and how all-trans retinal photoproduct can regenerate 11-cis. Both the usage of the RPE visual cycle and the photoisomerization of all-trans retinal to 11-cis by melanopsin itself are supported by evidence.

Invertebrate opsins and the melanopsin protein have similar sequences and functional properties.

The opsin. Melanopsin and invertebrate rhodopsins have more sequence in common than vertebrate rhodopsins do [12]. Invertebrate photoreceptors share some characteristics with ipRGC photosensitivity (Box 2).

In particular, photoactivation causes a brief increase in cytosolic Ca2+ levels [14,15]; ipRGCs depolarize upon light activation; and the photocurrent produced by ipRGCs displays a voltage-current relationship that is similar to that of the

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transient receptor potential (TRP) class of inward-rectifying cation channels [45].Additionally, mice with loss-of-function mutations in vertebrate rhodopsin signaling components, such as a downstream G protein (Gnat/), the signaling intermediate phosphodiesterase (Pde6b/ or Rd1), and an effecter channel (Cng3/), nonetheless exhibit complete melanopsin phototransduction [8, 19]. As a result, many blind people who have mutations in rhodopsin signaling elements likely nonetheless have normal ipRGC function.

It is practically impossible to use the same set of biochemical techniques that were effective in analyzing rhodopsin signaling mechanisms from native photoreceptors due to the dearth of ipRGCs. Instead, heterologously generated mammalian melanopsin and native Xenopus melanopsin in melanophores have served as crucial beginning points for research into melanopsin function. In both systems, light-stimulated melanopsin activates Gaq/Ga11 (Box 2), which then sends a signal through PLCb to cause the opening of an ion channel of the TRP class and an increase in cytosolic Ca2+. Native ipRGCs are anticipated to employ a similar signaling cascade. The Gq/G11 class of G proteins and PLCb can be specifically inhibited to prevent the melanopsin-mediated photocurrent in ipRGCs [48].Additionally, ipRGCs activated by light experience a rise in cytosolic Ca2+ [49], and the melanopsin photocurrent exhibits properties unique to the TRP class of ion channels [45]. These findings suggest that melanopsin uses a downstream signaling pathway different from the rod/cone signaling pathway found in vertebrates, one that is similar to the Drosophila rhodopsin.

Gq/G11 class G proteins as well as PLCb suppression [48].

The effecter G protein, the signal-amplifying cascade controlled by PLC, and the effecter ion channels are all essential parts of the melanopsin signaling cascade, and they are all encoded by functionally redundant family members that are expressed in practically all mammalian cells. Several GPCRs can also signal promiscuously via downstream signaling cascades and unfavorable G proteins.Thus, pure melanopsin also opens cyclic nucleotide-gated (CNG) class of channels [30] and activates the transducin class of G proteins (Gt) [50], both of which are downstream effectors of the vertebrate rhodopsin cascade. This suggests that melanopsin-initiated photoresponses might not entirely disappear upon the absence of any one signaling component.

On the other hand, melanopsin that is produced ectopically in any mammalian cell is likely to activate a signaling cascade. RGCs become light sensitive and exhibit characteristics akin to those of native ipRGCs when melanopsin is expressed ectopically in them [51]. Thus, the possibility for using melanopsin as a therapeutic optogenetic tool (Box 3) for treating various human ailments, such as blindness, is increased.

Box 2

illustrates important distinctions between rhodopsin phototransduction in vertebrates and invertebrates.

In vertebrates (Figure Ia), light-activated metarhodopsin activates a phosphodiesterase (PDE) that hydrolyzes 3'-5' cyclic guanosine monophosphate (cGMP) to 5' cGMP. This class of G protein is susceptible to pertussis toxin. The cyclic nucleotidegated (CNG) ion channels close as a result of the light-activated hydrolysis of cGMP, which also causes the photoreceptor cells to become hyperpolarized. In contrast, the pertussis toxin-resistant Gaq class of G proteins (Figure Ib) activates the phospholipase C-b (PLCb) enzyme to start the invertebrate cascade. Phosphatidylinositol-4,5-bisphosphate (PIP2) is converted to inositol-1,3,5-triphosphate (IP3) and diacylglycerol (DAG) by activated PLCb. Polyunsaturated fatty acids (PUFA) are created through further catalysis of DAG.The complicated events that follow PLC activation may involve the signaling intermediates IP3, DAG, and PUFA to open transient receptor potential (TRP) cation channels, which cause an inflow of Na+ and Ca2+ and membrane depolarization (reviewed in [113]). By releasing Ca2+ from Ca2+ storage, IP3 can also cause a rise in cytosolic Ca2+ levels [23].

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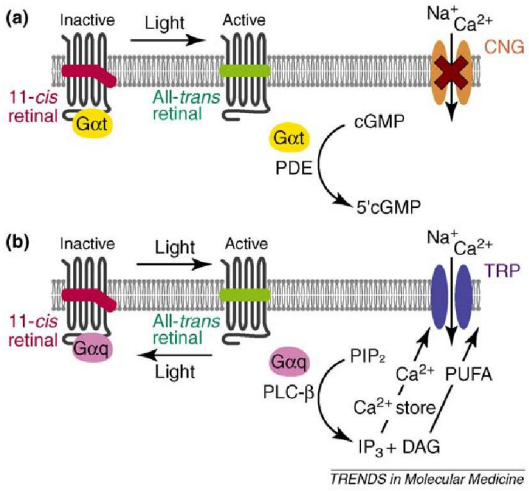

Figure I. Phototransduction mechanisms of classical vertebrate and invertebrate rhodopsins.
The invertebrate rhodopsin phototransduction signaling cascade (b) is different from the vertebrate rod/cone opsin phototransduction signaling cascade (a).

ipRGC photoresponses

IpRGCs contain exclusive qualities that are not shared by other photoreceptor cells, in addition to the distinct chromophore usage and signaling capabilities of melanopsin. Based on their signaling characteristics and neuroanatomy, up to 20 different types of RGCs in the mammalian retina can be differentiated [52]. The expression of the protein melanopsin and the resulting inherent photosensitivity are the distinguishing characteristics of ipRGCs in various species. Up to 3000 RGCs out of 1.5 million in each human eye exhibit positive formelanopsin staining [53].

Melanopsin immunostaining does not exhibit any regional preference within the cell, in contrast to the regionally concentrated rod/cone opsins in classical photoreceptor cells instead, almost uniform melanopsin staining is seen along the soma, dendrites, and, to some extent, in the axons of ipRGCs. [13];

The intrinsic photosensitivity of ipRGCs sets them apart from rod/cone photoreceptor cells because ipRGCs have a high threshold for activation, a lengthy latency to respond, and a long recovery time [15].Such response properties enable the ipRGCs to perform as irradiance detectors by integrating light information over prolonged illumination. Melanopsin responds slowly, but the exact reason why is yet unknown. Melanopsin has proved that it is at least as sensitive as conventional rod/cone photopigments by single-photon responses [41]. However, in contrast to conventional vertebrate or invertebrate photoreceptors, where the photopigments and downstream signaling components are concentrated in subcellular compartments, the diffuse distribution of melanopsin in the ipRGC membrane and of other signaling components in ipRGCs likely contributes to the sluggish response. A slow response qualitatively similar to melanopsin is produced when Drosophila Rh1 rhodopsin, one of the quickest responding photopigments, is expressed ectopically in mammalian neurons together with its downstream signaling components [55].

The ipRGCs transduce rod/coneinitiated light responses just like other RGCs do [56]. Primate ipRGC recordings reveal different rod, cone, and melanopsin-initiated responses [57]. Rods typically detect light in low-light situations (scotopic circumstances), and the rod-initiated light response depolarizes ipRGCs and sets off action potentials that are sustained for the duration of the light pulse. A progressive rise in light intensity within the rods' working range is accompanied by an increase in ipRGC firing. The rods bleach when the light intensity rises to levels experienced throughout the day. Cones and melanopsin-initiated light responses are both identified in ipRGCs under such lighting.At the beginning and end of light, the L (long wavelength) and M (medium wavelength) cone-initiated light signals transiently depolarize the ipRGCs and hence, but are unreliable for encoding light intensity over extended periods of time. dependable encode lights on or off. After a few milliseconds of cone-initiated reaction, the intrinsic melanopsin-mediated photoresponses start, and they continue during illumination. Rods, L and M cones, as well as ipRGCs are activated ("on"), and S (short wavelength) cones cause a "off" response. The intrinsic persistent melanopsin response is expected to prevail over the

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S-dependent off response in conditions of natural daylight, though. Overall, the primate ipRGC responses predict that rodinitiated light signals are likely to support NIF responses in low light (approaching the limit of human vision), whereas melanopsin-initiated responses tonically encode light intensity information and support NIF responses in natural daylight [57].cone-initiated (short wavelength) and M (mid wavelength),Consequently, coneto maintain appropriate NIF responses under daylight light levels in mice, responses alone are insufficient [58]. Cones and melanopsin play important roles in NIF responses, according to a recent human study [59]. Cone signals are just as effective as melanopsin signals for suppressing pineal melatonin secretion at the start of a prolonged strong light pulse.
Melanopsin serves as the primary NIF photopigment under natural long-duration, high-intensity light, while the cone contribution gradually decays exponentially over time. Both cones and melanopsin contribute to determining the phase of the human circadian clock in conditions of moderate light.At the beginning and end of light signals, the ipRGCs transiently depolarize.
How do the melanopsin, rod, and cone photoresponses integrate? Figure 3 shows what happens in mice when the precise ablation of ipRGCs results in the nearly complete loss of all NIF responses while keeping the IF responses mostly intact [78–80]. This means that rod- and cone-initiated light signals that are intended to elicit NIF responses are primarily conveyed through ipRGCs, which act as the primary cellular node integrating light responses from all three photopigment systems. It is yet unknown, nevertheless, whether melanopsin expression in ipRGCs has an impact on how it functions in mediating rod/cone-initiated responses. For instance, does melanopsin merely add to the effects of the outer retina or does it somehow improve the effects of rod/cone-initiated responses? In conclusion, ipRGCs serve as the primary cellular framework for NIF responses since the net light signal that passes through them supports the majority of NIF reactions.

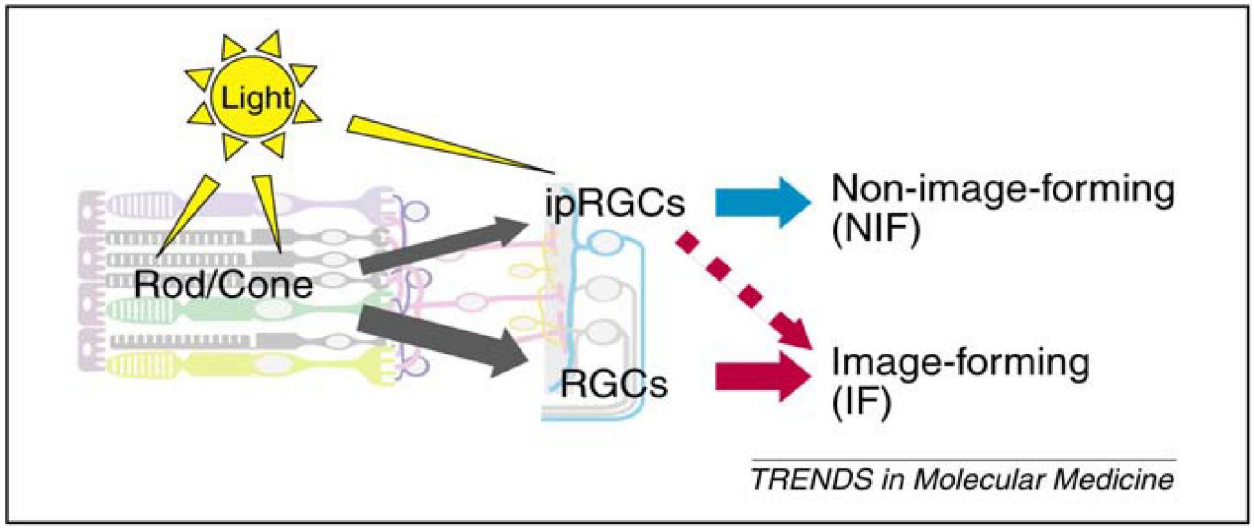

Figure 3 shows where the signal integration takes place: the ipRGCs
Through many synaptic connections, the rod and cone photoreceptors of the outer retina communicate with the RGCs of the inner retina. Through their axonal extensions, the RGCs in turn transmit visual signals from the eye to the brain. The light information coming from the rods and cones is only transferred by ipRGCs for NIF visual activities. The ipRGCs serve as the nodes for integrating rod- and cone-initiated photoresponses and melanopsin responses. ipRGCs are probably going to take part in the IF vision via two different possible ways. They also have an impact on the amacrine cells, which respond to dopamine, in the retina [95].which then influence how the rod/cone-initiated signals adjust to long-term illumination. The dorsal lateral geniculate nucleus (LGN), which has substantial innervation from other RGCs, gets projections from the ipRGCs as well [57].

Box 3. Optogenetics

Optogenetics is the study of how to explore or modify biological function by optically stimulating a light-sensitive protein.The production of a bacterial or algal rhodopsin in a particular type of neuronal cell and accurate millisecondscale optical stimulation are common uses. The high-speed opening and closing of the channel at the rate of

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millisecond-scale light pulses is made possible by the fact that these rhodopsins are a natural hybrid between a light-sensitive opsin and an effecter channel. Melanopsin has distinct advantages for particular uses but is unsuited for such widespread optogenetic applications because to its slow reaction. Melanopsin can therefore be utilized to simulate Gq/G11 class GPCR signaling. Melanopsin-related signaling processes raise the intracellular Ca2+ level. High intracellular Ca2+ levels cause cyclic AMP/Ca response element-binding protein (CREB) to become phosphorylated, which then causes light to activate the transcription of CREB targets [114].Each phase of the multistep intracellular signaling cascade used by melanopsin results in a large signal amplification by nature. In mice with severe rod/cone cell degeneration, melanopsin is expressed by recombinant adeno-associated viruses, which recovers some visual functions under standard indoor lighting conditions [51]. Some visual abilities are also restored by channel rhodopsin use, but only in high intensity light conditions similar to midday sunlight [115]. These early accomplishments, together with the fact that humans naturally express melanopsin, give rise to the possibility that melanopsin could end up being the preferred tool in various optogenetics-based gene therapy techniques.

Ontogeny, architecture and projections of ipRGCs

In contrast to melanopsin expression, which starts in utero long before the rod/cone photoreceptors are completely functional, ipRGCs are born alongside other RGCs in rats [60]. Because premature newborns born after 33 weeks clearly exhibit pupil constriction in response to light, it is obvious that the melanopsin system is likewise completely functional in humans in utero [61]. It is still unclear whether genetic circuitry determines the ipRGC identity or melanopsin expression. The master transcription factors Math5 and Brn3, which control RGC differentiation, also control the fate of ipRGC cells [62–64], albeit it is still unknown which downstream regulators control ipRGC identity or melanopsin expression.

Many hints about the functioning of ipRGCs can be found in their neuroanatomy. IpRGCs are among the RGC cell types in the primate retina with the biggest somata and the greatest dendritic arborization [57]. The dendrites of ipRGCs heavily overlap one another, in contrast to most other RGC cell types, which are organized in a nonoverlapping cobblestone pattern [13,65]. Melanopsin-expressing RGCs have been divided into (at least) three subtypes known as M1-M3 by analyzing the shape of their dendrites and their sensitivity to light (Figure 1b; reviewed in [66]), while a recent work questions whether the M3 subtype actually constitutes a distinct cell type. Regarding threshold sensitivity, the size of the responses, and deactivation rates, mouse ipRGC physiological responses likewise show notable variability [67].In mouse retinas, the M1 and M2 cell types display different photosensitive characteristics [68]. It is still unknown whether this diversity is conserved in primates despite these thorough descriptions of morphological and physiological diversity and whether each cell type has a particular function.

In the inner plexiform layer (IPL), dendrites of the predominate M1 and M2 subtype ipRGCs stratify in either the off or on sublaminae where they receive synaptic input from bipolar and amacrine cells [69,70]. The regular operation of the melanopsin system will be greatly impacted by factors that specify dendritic stratification in the retina or factors that determine RGC projections to the target brain regions. Mice lacking the essential component Dscam, which defines dendritic stratification and spreading, consequently display the abnormal dendritic architecture of ipRGCs [71].

ipRGCs have intriguing projections, in contrast to the majority of other RGCs whose axons cross the optic chiasma and generally project to the contralateral side of the brain.IpRGCs from one eye almost equally innervate the left and right halves of the suprachiasmatic nucleus (SCN), the major circadian brain region, just after the optic chiasma. Like other RGCs, ipRGCs also project contralaterally to areas of the brain that either directly or indirectly control other NIF processes outside of the SCN.These areas include the olivary pretectal nucleus (OPN), which regulates pupil constriction, and the intergeniculate leaflet (IGL), which indirectly synchronizes the circadian clock.The fact that the SCN and OPN both receive ipRGC input primarily suggests a distinct axon guiding mechanism mediates such strong connections. Sparse projections from ipRGCs also reach a number of additional brain regions. They consist of the habenula, subparaventricular zones, ventrolateral preoptic nucleus, and lateral hypothalamus. These projections are most likely to act as a mediator between light exposure and changes in physiology, behavior, and sleep regulation. The ipRGC regulates pineal melatonin with multisynaptic projections [76].The functional relevance of ipRGC projections has been validated by phenotypic analyses of mice lacking melanopsin or those with the targeted ablation of ipRGCs, which likewise show specific deficits in the light-dependent behaviors supported by these brain regions (reviewed in

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[66]). It is suggested that the recently reported sparse ipRGC projections in the posterior thalamus, which were found next to dura-sensitive thalamocortical neurons, explain the mild exacerbation of migraine pain [43].

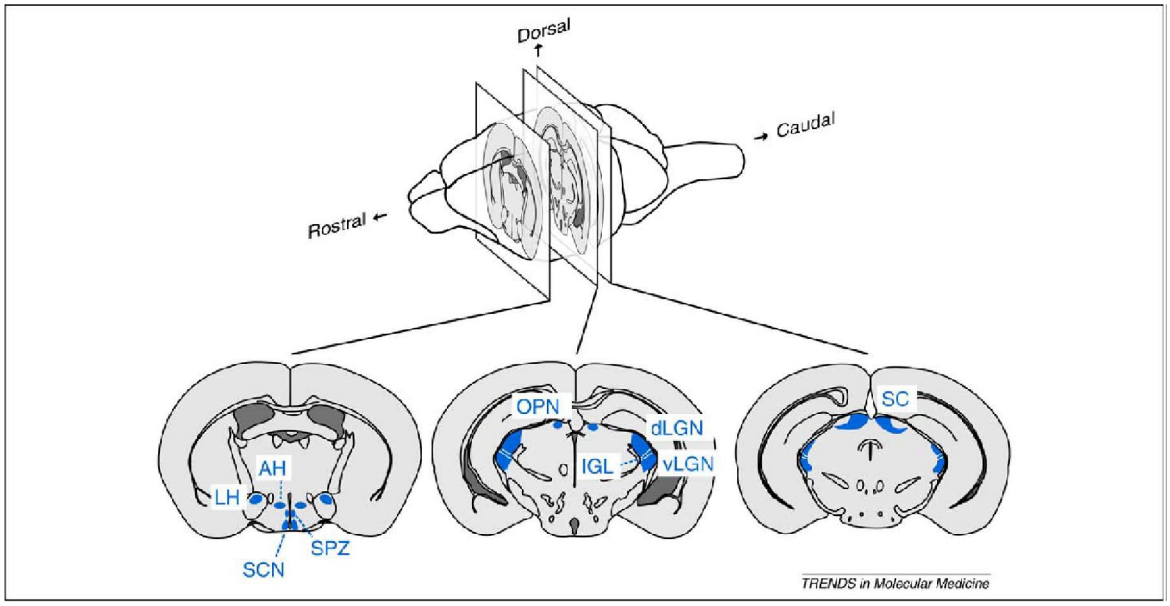

Figure 4 shows the ipRGCs' central projections.

a schematic representation of the brain areas that are innervated by ipRGC axons. OPN: olivary pretectal nucleus; IGL: intergeniculate leaf; dLGN: dorsal lateral geniculate nucleus; vLGN: ventral lateral geniculate nucleus; SC: superior colliculus; SCN: suprachiasmatic nucleus; LH: lateral hypothalamus; AH: anterior hypothalamus; SPZ: subparaventricular zone.

Additional ipRGC brain targets have been found thanks to new mouse lines that completely mark the majority of ipRGCs.Significant axonal projections from ipRGCs are directed onto the superior colliculus (SC), as well as the ventral and dorsal lateral geniculate nuclei (vLGN and dLGN) [77] (Figure 4).The SC and LGN serve as the main relay centers for IF vision and both receive substantial innervations from other RGCs.The ape brain also contains ipRGC projections to the LGN [57]. As a result, some blind people with severe rod/cone photoreceptor loss [11] have basic visual awareness.ipRGC projections to the LGN and SC may offer brightness information for IF vision in healthy persons. In conclusion, ipRGCs substantially innervate a number of brain areas responsible for modulating NIF responses. They also innervate the LGN and SC, where they are probably encoding irradiance information for IF vision.

The melanopsin system's genetics

Rodent genetics has been a major source of information for us regarding the function of melanopsin and ipRGCs in NIF responses.

The roles of photopigments and ipRGCs in NIF responses have been defined by comparative investigations of light-dependent behaviors in mice lacking melanopsin (Opn4/), rod/cone function, or ipRGCs. The majority of acute NIF reactions that are triggered by high-intensity light or long-lasting NIF responses are generally diminished in Opn4/ mice. These include pupil constriction, general activity, sleep, and the modification of the circadian clock phase by light (reviewed in [66]). Mice lacking both melanopsin and functioning outer retina photoreceptors entirely lose these photoresponses [8,19].This suggests that rod/cone photoreceptors can make up some of the lost melanopsin protein.In mice with intact and fully functional rod/cone photoreceptors, specific acute or progressive loss of ipRGCs also results in the loss of NIF light responses (Figure 3), establishing ipRGCs as the primary carriers for transmitting the light information coming from both melanopsin and outer retina photoreceptors [78-80].

The relative contributions of rods and cones in NIF responses are being clarified by further mice models that specifically disable rod or cone photoreceptor function [58,81]. As anticipated, some NIF responses, such as circadian photoentrainment, can be partially supported by both rods and cones [16]. Surprisingly, cones appear to have no effect on circadian photoentrainment, even at photopic light levels. These mouse genetic investigations confirm the general

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response characteristics of primate ipRGCs, which show that a rod-initiated response permits irradiance encoding in low light, while cone transient responses are insufficient to encode irradiance levels in high light.As a result, nocturnal rodents and diurnal primates, including humans, have substantially preserved roles for rod, cone, and melanopsin in NIF responses.

The study of mouse genetics has also provided insight into possible signaling processes in ipRGCs. Mice lacking the unusual protein kinase C (PKCz) mimic the Opn4/ mice's decreased photosensitivity. The potential that PKCz is essential to the melanopsin-signaling cascade is increased by the expression of PKCz in ipRGCs [82].The same information about the potential downstream neurotransmitters in ipRGCs has also been gleaned from mice research. Pituitary adenylate cyclase-activating peptide (PACAP) is a neuropeptide that is also expressed by melanopsin-expressing cells [53, 83, 84], and the SCN has PACAP receptors [73, 85].While rats lacking PACAP or the PACAP receptor show a decreased responsiveness of the circadian clock to a phase resetting pulse of light, exogenous administration of PACAP at low doses can phase shift the SCN clock [86–88]. Glutamate, which is present in ipRGCs as well, is most likely the mediator of the residual circadian photosensitivity in PACAP mutant mice [89]. According to [90] and references therein, SCN neurons contain glutamate receptors, and exogenous glutamate administration to SCN slice culture can imitate light-induced phase shifts in the SCN clock [91,92]. Both PACAP and glutamate receptors are potent therapeutic targets for a number of disorders [93,94]. As a result, particular pharmacological agents that affect the PACAP and glutamate signaling pathways may have a big effect on how NIF responses are regulated.

Visual responses' interaction between IF and NIF

Several animal models have shown NIF responses and rod/cone-mediated IF vision as being mostly independent of one another; nevertheless, new data point to an interplay between these two systems at different levels. Both in the retina and LGN, the melanopsin system has the ability to modify traditional IF vision. The signal from the ipRGCs to the dopaminergic amacrine cells may serve as the foundation for the visual system's adjustment to changes in light intensity [95]. According to ipRGCs' innervations of the LGN in primates [57] and rodents [77], the melanopsin system may immediately communicate information about ambient light intensity to the IF visual system.

The melanopsin system and the outer retina both have potential regulatory levels. The quantity of melanopsin protein and, subsequently, the time of activity rest in mice can be affected by the general dysregulation of retinoid availability, as has been demonstrated in Rpe65/ and Lrat/mice [36,37,96].As we gain a better understanding of the relative roles of rods and cones in NIF responses, it may have a profound impact on human health. Numerous illnesses of the outer retina that result in blindness start with a selective loss of RPE, rod, or cone function and develop to a large amount of outer retinal cell death. The surviving retina undergoes significant remodeling over the course of months and years, during which time the relative makeup of cell types and their connections alters [97]. Older rats with outer retinal degeneration have also shown substantial modification of ipRGC dendritic structures in the retina [98]. Therefore, the melanopsin system may be affected in a complex and gradual manner by a number of degenerative illnesses of the outer retina.

Applications that enhance health

Now that melanopsin has been identified, it is possible to mechanistically explain how light influences human physiology, behavior, and sleep. As a result, the efficient use of light in enhancing quality of life now presents new opportunities for interdisciplinary work among doctors and researchers of numerous scientific fields that have up until now largely remained nonoverlapping: circadian/endocrine biology, vision science, sleep and neuroscience, and architectural lighting.The melanopsin photosystem can have an immediate impact on human health and disease in a number of ways, including (i) modifying disease diagnosis methods based on an assessment of the melanopsin system; (ii) changing medical procedures to address melanopsin-mediated photoresponses; (iii) developing pharmacological interventions for NIF responses; (iv) identifying gene alterations in patients; and (v) managing light exposure at work, home, and caregiving facilities.

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Melanopsin system diagnostic techniques

According to rodent research, disturbed melanopsin signaling may be the root cause of a number of human disease problems, including sleep disorders, depression, seasonal affective disorders (SADs), aversion to light, and light-induced migraine headache [43]. It is essential to have accurate diagnostic techniques to measure melanopsin function before attempting to determine whether the melanopsin system contributes to these illnesses.

However, almost all of the retinal diagnostic techniques used today assess the structure and performance of the outer retina's rod and cone photoreceptors. These methods are inappropriate for assessing the function of the ganglion cell layer (GCL) of the inner retina's sparsely scattered ipRGCs. A PLR assay would be a potential approach. It is now well known that melanopsin specifically contributes to the persistence of pupil constriction for several seconds after a transient pulse of light in rats and primates [7,18,99].To specifically evaluate melanopsin function in pupil constriction, a recent study was successful in adjusting the spectral conditions. Additionally, in one type of blindness (Leber's congenital amaurosis), the melanopsin response is diminished, whereas in an other type of blindness, the response is normal or even augmented [100]. A similar PLR response can also be used as a proxy for gauging the severity of glaucoma, another condition that gradually destroys RGCs and causes blindness. In conclusion, the assessment of ipRGC function serves as a starting point for further categorizing blindness into patients who have completely lost both their NIF and IF visions, as well as those who have lost only their IF vision.This classification will help establish whether some blind individuals with normal ipRGC function might benefit from retaining a higher quality of life than those who have no ability to perceive light.

Practices in medicine

The selection of cataract lenses, pharmacological interventions targeting the retinoid pathway for the treatment of other diseases, the choice of surgical bilateral enucleation as a prognosis for certain eye diseases including retinoblastoma, and the evaluation of gene therapy for improvement in quality of life are just a few medical procedures that can now be evaluated in the context of melanopsin function. In the blue spectrum of visible light, for instance, the human lens gradually loses transmittance, so that a 75-year-old's lens transmits 2-log units less light at 480 nm than a 5-year-old's lens [101,102].Therefore, providing elderly patients with enough exposure to strong light is particularly crucial. Furthermore, it may be ideal to implant an intraocular lens with minimal transmittance in the harmful near-UV range but sufficient transmittance in the blue range to restore function in order to enhance visual function, optimally activate the melanopsin system, and subsequently improve sleep quality in elderly patients.

Pharmaceutical assistance

Melanopsin and rod/cone phototransduction pathways differ from one another, which has inspired theories on how to control signaling flux through ipRGCs to treat human illnesses that are influenced by lighting. But it's still not clear where to intervene. Modulating melanopsin or a downstream signaling element in ipRGCs without disrupting the rod/cone signaling pathway would be the optimal course of action. Potentially useful substances should simulate pharmacological light or darkness and either activate or inhibit the light flux through ipRGCs. Inhibitors would imitate darkness and prevent the light from suppressing melatonin, while activators would imitate light and offer a novel pharmacological intervention for a mood-lifting effect.Additionally, the discovery that ipRGCs may mediate the light exacerbation of migraine pain recently made [43] offers the prospect that pharmacological darkness, either by alone or in combination with other medications, may provide a unique approach to treating pain in healthy and blind patients.

Patient-derived gene and mechanism discovery

A variety of human diseases may have an underlying deficiency in melanopsin function, according to the phenotypes of mice with altered signaling flow via the melanopsin system. The melanopsin system may be impacted by a variety of mechanisms and genes, including melanopsin, putative downstream signaling components, factors affecting ipRGC differentiation, connectivity to specific brain regions mediating NIF responses, and genes in the outer retina that may affect ipRGC function. We may discover genes and pathways connected with the melanopsin system as the cost of genome sequencing decreases and genetic association studies identify loci linked to depression, SADs, and sleep disorders.This kind of early success has previously been shown to work. A small fraction of SAD patients have a

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particular mutation in melanopsin that alters an amino acid [103]. The short winter days often trigger a sort of depression in SAD patients, and many of them find light treatment (exposure to blue-enriched light) to be beneficial. This emphasizes the importance of light signaling for increased alertness in humans.

Management of Light

In industrialized countries, the general public is increasingly exposed to long stretches of artificial light that last well into the night [104]. Additionally, most hospitals and care facilities frequently offer lighting that is available around-the-clock. While daylight-like light during the day may be advantageous, similar light at night can negatively impact the circadian clock and related physiologies [105]. Manufacturers of lighting and architects are being prompted by this to adapt dynamic lighting for the home, office, and care facilities.Despite these opportunities to use understanding of melanopsin function to enhance human health, substantial obstacles still exist. Despite the fact that melanopsin is expressed in the retina and is therefore a topic of vision science, the primary effects of disrupted melanopsin signaling are likely to be sleep disturbances, mood disorders, and their ensuing effects on metabolism, which are outside the purview of vision science. Furthermore, patients frequently require immediate attention for these illnesses because of their complex etiologies. However, the evaluation of the melanopsin system in the retina is clearly a task for vision experts. Alternately, sleep specialists and psychiatrists could start questioning how patients' sleep and mood issues are related to illumination or the melanopsin signaling system.

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