Retinal light perception and biological rhythms: The role of light in sleep and mood from an ophthalmic perspective (Review)

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Abstract. Light is the paramount environmental signal for the entrainment of endogenous circadian rhythms. Its non-visual effects, mediated by the retina, exert a profound control over human sleep, mood and systemic physiological homeostasis. Beyond its canonical function in image formation, the retina operates as a primary irradiance detector through a specialized class of neurons, the intrinsically photosensitive retinal ganglion cells (ipRGCs), which utilize the photopigment melanopsin. These cells convey environmental light information directly to the suprachiasmatic nucleus (SCN), the brain's master circadian pacemaker, thereby synchronizing the body's internal timekeeping with the external solar cycle. Compelling evidence demonstrates that the spectral quality of light, particularly within the short-wavelength blue range, potently modulates neuroendocrine and neural systems via the ipRGC pathway, governing melatonin synthesis, the architecture of the sleep-wake cycle and affective regulation. The modern light environment, characterized by ubiquitous artificial light at night and pathological states of light perception resulting from ophthalmic diseases such as glaucoma and retinal degenerations, can severely disrupt this synchronization. The consequent circadian misalignment is a significant etiological factor in sleep disorders, depressive symptoms and other systemic morbidities. The retina's integral position within the light-rhythm-behavior axis is thus a critical nexus between the visual system and systemic physiology. In addition, the present study outlined the nitric oxide-cyclic GMP signaling axis in SCN as a critical mediator of photic entrainment. This review provided an in-depth analysis from an ophthalmic perspective, synthesizing evidence from animal models and human studies to dissect the complex molecular, cellular and network-level mechanisms of retinal circadian regulation, explore how aberrant photic signaling impacts sleep and mood and critically evaluate the potential of targeted interventions such as light therapy and spectral management in the context of rhythm-related disorders.

Contents

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1. Introduction

Light, the most powerful environmental cue, or *zeitgeber*, is indispensable for synchronizing the brain's endogenous biological rhythms with the 24-h terrestrial day. This synchronization underpins temporal organization across all levels of physiology, profoundly influencing sleep architecture, affective state and metabolic homeostasis (1). While the human retina has been traditionally conceived as the exclusive domain of image-forming vision, a paradigm shift has illuminated its central role in mediating a suite of non-image-forming (NIF) responses to light. These vital functions, including circadian photoentrainment, neuroendocrine modulation and pupillary control, are primarily orchestrated by a unique population of intrinsically photosensitive retinal ganglion cells (ipRGCs) (2,3). These neurons, expressing the

blue-light-sensitive photopigment melanopsin, form a direct conduit to key subcortical brain regions, most notably the suprachiasmatic nucleus (SCN) in the hypothalamus, which serves as the master circadian pacemaker (4).

From an advanced ophthalmic and neuroscience perspective, the retina is a highly sophisticated interface between environmental photic information and the central nervous system's timing machinery (5). Operating in concert with classical photoreceptors (rods and cones), ipRGCs detect ambient illuminance and transduce this information into neural signals that govern the sleep-wake cycle, regulate the secretion of the chronobiotic hormone melatonin and directly modulate brain circuits involved in mood (6). Pathological disruption of this pathway, arising from degenerative ophthalmic diseases, the physiological process of aging, or the pervasive alteration of our light environment by modern technology, can precipitate a state of circadian desynchronization, leading to impaired sleep quality, affective disorders and a host of other systemic health problems (7).

A growing body of evidence from complex animal models and human clinical studies highlights the profound vulnerability of the NIF system in the context of retinal pathology (8-10). Diseases such as glaucoma, which leads to the progressive loss of retinal ganglion cells, and retinal degenerations such as retinitis pigmentosa, can selectively or disproportionately compromise ipRGC function (11). This damage results in a cascade of downstream consequences, including circadian arrhythmia, severely disrupted sleep architecture and mood instability that transcends the psychological effect of vision loss itself. Conversely, the precise understanding of these pathways has unlocked novel therapeutic possibilities. Targeted manipulation of light exposure, through spectrally-tuned light therapy or advanced spectral filtering technologies, offers the potential to strategically modulate retinal input to circadian centers, heralding new frontiers in both ophthalmic and behavioral medicine (12), The present review synthesized current, in-depth knowledge of retinal light perception and its complex implications for circadian biology, sleep and mood, with a specific focus on the intricate mechanisms and clinical significance in ophthalmic disorders.

2. The molecular and cellular mechanisms of retinal light perception

The retina's capacity to inform the brain about the presence and quality of environmental light is mediated by a sophisticated and heterogeneous assembly of photoreceptive and neuronal cells (13). While the roles of rods and cones in image formation are well-established, a deeper understanding of the retina's non-visual functions requires a detailed examination of the intrinsic photosensitivity of ipRGCs, their unique molecular machinery and their intricate integration within the retinal network (14).

The cellular architecture for photoreception includes not only the classical photoreceptors but also the 1-3% of retinal ganglion cells that are ipRGCs (15). These cells express the G-protein coupled receptor photopigment melanopsin and can function as autonomous light detectors. This intrinsic photosensitivity is fundamentally different from that of rods and cones (13). Melanopsin phototransduction is a depolarizing cascade initiated by the activation of a Gq/11-class G-protein, leading to the engagement of phospholipase Cβ4. This enzyme hydrolyzes phosphatidylinositol 4,5-bisphosphate into inositol trisphosphate and diacylglycerol. The subsequent opening of specific transient receptor potential canonical (TRPC) channels, primarily TRPC6 and TRPC7, permits a sustained influx of Na^+ and Ca^{2+}, causing a prolonged membrane depolarization and a tonic increase in the cell's action potential firing rate (11). This sustained response is ideal for encoding ambient irradiance over long timescales, a critical feature for circadian signaling. A key feature of melanopsin is its function as a bistable pigment; its all-trans-retinal chromophore can be photoisomerized back to the 11-cis form by long-wavelength light, allowing for regeneration within the cell, a stark contrast to the enzymatic recycling pathway required for rod and cone opsins (16,17).

The ipRGC population is not monolithic. In mammals, at least six subtypes (M1-M6) have been delineated based on distinct morphological, molecular and functional characteristics (13). M1 ipRGCs stratify their dendrites in the OFF sublamina of the inner plexiform layer (IPL) and are defined by expression of the transcription factor Brn3b. They are the principal drivers of photoentrainment, forming the primary afferents of the retinohypothalamic tract (RHT) to the SCN (18). M2 and M4 cells stratify in the ON sublamina of the IPL, co-express the transcription factor Tbr2 and contribute markedly to the pupillary light reflex via projections to the olivary pretectal nucleus. M4 cells, in particular, have large dendritic fields and are also implicated in contrast sensitivity for conscious vision (4). Other subtypes, such as M5 and M6, project to a diverse array of over 40 distinct subcortical targets, including limbic structures such as the amygdala, bed nucleus of the stria terminalis and lateral habenula, providing a direct anatomical substrate for light's influence on mood, fear and motivation. This remarkable projection diversity means that the retina disseminates parallel streams of photic information to functionally distinct brain circuits (8).

Crucially, ipRGCs do not operate in isolation. They are deeply embedded within the retinal circuitry, acting as complex integrators of both their own intrinsic photoresponse and extrinsic signals relayed from rods and cones through specific amacrine and bipolar cell pathways. For example, ipRGCs receive significant input from ON-cone bipolar cells, allowing them to respond robustly to daylight. Rod signals are conveyed primarily through AII amacrine cells and subsequent gap junctions, conferring high sensitivity to light at night (19). This integration allows ipRGCs to encode light information across an astonishing 12-log-unit range of intensities. The spectral sensitivity of this integrated system is complex, but the intrinsic (15) response, with its peak sensitivity to blue light ~480 nm, is the dominant driver of NIF functions such as circadian resetting and melatonin suppression (20) This specific wavelength dependency is the biophysical basis for the potent effects of blue-enriched light from modern sources on human physiology (21).

Ophthalmic diseases profoundly alter these intricate mechanisms. In glaucoma, the progressive apoptosis of RGCs includes the loss of ipRGCs. Studies indicate that different ipRGC subtypes may have differential vulnerability, potentially explaining the specific patterns of NIF deficits observed

Table I. Key cell types and photopigments involved in non-image-forming light perception.

Cell type	Marker/photopigment	Main function	Projection target(s)
Rods	Rhodopsin	Low-light vision, support NIF via ipRGCs	Bipolar cells, ipRGCs (indirect)
Cones	Photopsins	Color, daylight vision, input to NIF	Bipolar cells, ipRGCs (indirect)
M1 ipRGCs	Melanopsin (OPN4)	Circadian photoentrainment	SCN, OPN
M2-M6 ipRGCs	Melanopsin (OPN4)	Pupillary reflex, mood regulation, etc.	OPN, LHb, mPFC, other targets
Amacrine/Bipolar cells	Various	Intraretinal signal integration	ipRGCs

NIF, non-image-forming; ipRGCs, intrinsically photosensitive retinal ganglion cells; SCN, suprachiasmatic nucleus; OPN, olivary pretectal nucleus; LHb, lateral habenula; mPFC, medial prefrontal cortex.

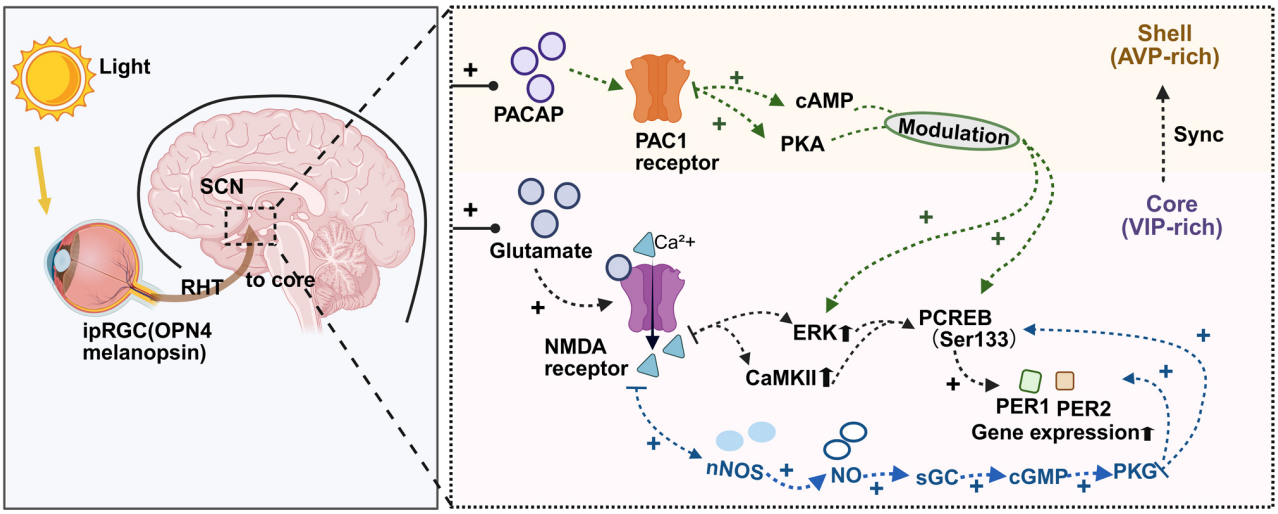

Figure 1. Retinal input and intracellular signaling underlying photic entrainment of the SCN. Light is detected by melanopsin-expressing ipRGCs in the retina and conveyed to the SCN via the RHT, which releases glutamate and PACAP. In SCN neurons, glutamate activates NMDA receptors, elevating Ca^{2+} and engaging CaMKII/ERK, which promotes CREB (Ser133) phosphorylation and PER1/PER2 expression. In parallel, Ca^{2+} activates nNOS and NO stimulates sGC to increase cGMP, activating PKG that further supports CREB phosphorylation and clock-gene induction. PACAP acting on PAC1 receptors modulates these processes and stabilizes entrainment. SCN, suprachiasmatic nucleus; ipRGCs, intrinsically photosensitive retinal ganglion cells; RHT, retinohypothalamic tract; PACAP, pituitary adenylate cyclase-activating polypeptide; NMDA, N-methyl-D-aspartate; CaMKII, calmodulin-dependent protein kinase II; CREB, cAMP response element-binding protein; period circadian protein homolog; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; sGC, soluble guanylyl cyclase; cGMP, cyclic guanosine monophosphate; PKG, protein kinase G; AVP, arginine vasopressin; VIP, vasoactive intestinal polypeptide.

in patients, such as impaired pupillary responses and severe sleep disturbances. In retinal degenerations such as retinitis pigmentosa, the loss of rods and cones functionally 'unmasks' the pure melanopsin-based photosensitivity of surviving ipRGCs (22,23) While these surviving cells can sustain circadian entrainment, the absence of rod and cone input severely reduces the overall sensitivity of the system and eliminates its ability to respond to rapid light changes, often leading to poorly entrained or free-running rhythms. These pathologies transform the retina into a model system for understanding how specific disruptions in photic signaling pathways lead to systemic neurobehavioral dysfunction (15). The main cell types and photopigments involved in NIF light perception are summarized in Table I.

3. The intricate relationship between the retina and circadian rhythms

The process of photoentrainment, the synchronization of the endogenous circadian clock to the 24-h light/dark cycle, is governed by a precise neuroanatomical and molecular dialogue between the retina and the SCN. This section delves into the detailed mechanisms of this critical interaction, from the specific neurochemistry of the RHT to the molecular clockwork within SCN neurons that is the target of retinal input (Fig. 1) (24,25).

The anatomical foundation of photoentrainment is the RHT, a monosynaptic pathway originating from a subset of ipRGCs, predominantly M1 cells, which terminates in the ventrolateral core region of the SCN. The principal neurotransmitters released by RHT terminals are glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP) (4). These transmitters have distinct but synergistic roles. Glutamate, acting on N-methyl-D-aspartate (NMDA) receptors, is the primary mediator of the acute, phase-shifting effects of light. Its release is proportional to the light intensity and duration, triggering rapid intracellular signaling. PACAP, acting on PAC1 receptors, plays a more modulatory role, enhancing the SCN's sensitivity to glutamate and being crucial for entrainment to full light-dark cycles and for the long-term stability of the clock (26).

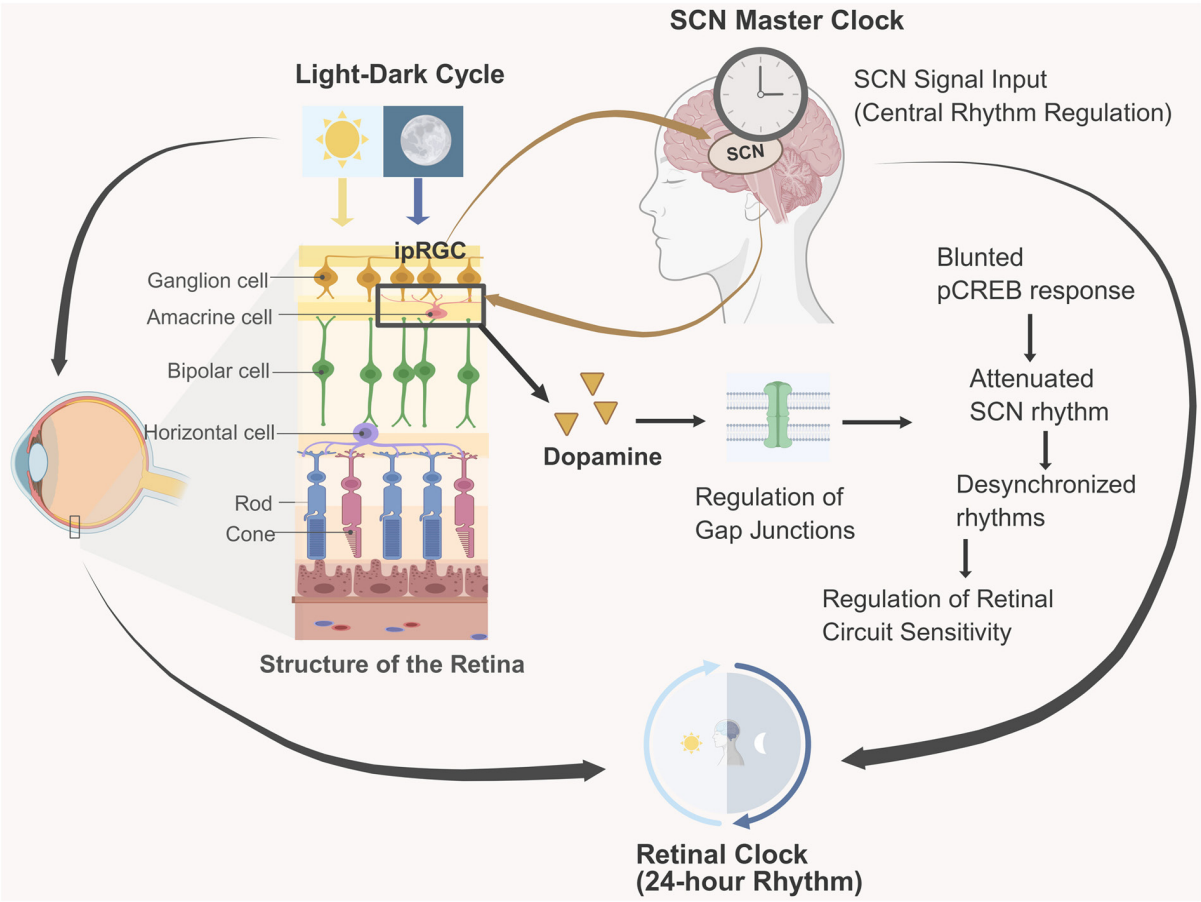

Figure 2. Interaction between retinal light perception, the retinal circadian clock and the central clock. Light is detected by ipRGCs and retinal circuits, triggering rhythmic dopamine release that modulates retinal sensitivity via gap junctions. ipRGCs convey light information to the SCN to synchronize central rhythms. In return, SCN signals regulate the autonomous retinal clock, which controls local gene expression and physiology in a 24-h cycle. This bidirectional system ensures coordinated circadian regulation within the retina and the whole organism. SCN, suprachiasmatic nucleus; ipRGCs, intrinsically photosensitive retinal ganglion cells; pCREB, phosphorylated cAMP response element-binding protein.

Upon light stimulation, the release of glutamate and PACAP in the SCN initiates a complex intracellular signaling cascade within postsynaptic SCN neurons (27). Glutamate-induced NMDA receptor activation leads to a significant influx of Ca^{2+}, which in turn activates multiple downstream pathways, including calcium/calmodulin-dependent protein kinase II (CaMKII) and the Ras/MAPK/ERK pathway. These kinases converge on the phosphorylation of the transcription factor cAMP response element-binding protein (CREB) at its Serine-133 residue (28). Phosphorylated (p-)CREB then translocates to the nucleus and binds to cAMP response elements in the promoters of the core clock genes *Per1* and *Per2*, rapidly inducing their transcription (29). This light-driven surge in *Per* expression is the molecular event that resets the phase of the SCN clock. A light pulse in the early subjective night advances the accumulation of PER protein, causing a phase delay, while a pulse in the late subjective night or early morning accelerates the declining phase of PER, leading to a phase advance (30).

The SCN itself possesses a sophisticated internal structure, comprising a ventrolateral 'core' and a dorsomedial 'shell.' The RHT innervates the core, which is rich in neurons expressing vasoactive intestinal polypeptide. These core neurons are the primary recipients of light information. They then synchronize the much larger population of neurons in the shell, which express arginine vasopressin and are considered the primary output neurons of the SCN (31). This core-shell network architecture allows the SCN to integrate the photic signal, generate a robust, consolidated rhythm and then broadcast this timing information to the rest of the brain and body (32).

Disruptions to this system via retinal pathology have profound consequences. In glaucoma models, the reduction in ipRGC density leads to a quantifiable decrease in RHT input to the SCN (33). This manifests as a blunted pCREB response to light pulses, attenuated amplitude of the SCN's overall electrical activity rhythm and, ultimately, the desynchronization of behavioral and hormonal rhythms, such as locomotor activity and melatonin secretion. In humans with advanced glaucoma, these central deficits are correlated with clinical reports of non-24-h sleep-wake disorder and depression (34). In cases of retinitis pigmentosa where cone and rod function is lost but ipRGCs survive, the SCN can still be entrained (35). However, the system's sensitivity is markedly reduced, requiring much higher irradiances of blue-enriched light to elicit a phase shift. This highlights the critical contribution of the classical photoreceptors in sensitizing the NIF system under normal conditions (36).

Furthermore, the retina itself harbors an autonomous circadian clock (Fig. 2). Clock genes are rhythmically expressed

in various retinal cell types, including photoreceptors and dopaminergic amacrine cells, regulating local physiological processes such as dopamine release, gene expression and metabolic activity in a 24-h cycle (37). This retinal clock is synchronized by both systemic signals from the SCN and the local light-dark cycle. Dopamine, released rhythmically during the day, acts as a key intraretinal signal that modulates gap junction coupling and adjusts the sensitivity of retinal circuits. This local timekeeping mechanism adds another layer of complexity, suggesting a bidirectional communication system where the retina not only signals time to the brain but also possesses its own intrinsic temporal organization that fine-tunes its function across the day-night cycle (38).

Light-evoked glutamatergic input from the RHT elevates postsynaptic Ca^{2+} in SCN neurons via NMDA receptors, which activates neuronal nitric oxide (NO) synthase (nNOS) and drives NO production (39). NO stimulates soluble guanylyl cyclase (sGC) to increase cyclic guanosine monophosphate (cGMP), engaging protein kinase G (PKG) pathways that facilitate phosphorylation of CREB and the rapid induction of *Per1*/*Per2*. Pharmacological inhibition of NOS or sGC diminishes light-induced phase shifts and *Per* transcription, whereas NO donors or membrane-permeant cGMP analogs enhance them (40). Thus, NO functions as a critical second-messenger amplifier that couples the initial RHT glutamatergic signal to the transcriptional machinery that resets the circadian clock. In parallel, intraretinal NO-produced by amacrine and other interneurons-modulates gap junction coupling and photoreceptor/bipolar signaling, shaping the irradiance code ultimately delivered by ipRGCs to the SCN (41).

4. Retinal light input and the neurobiology of sleep regulation

The regulation of the sleep-wake cycle is a complex interplay between a homeostatic process, which increases sleep pressure with time spent awake and the circadian process, which dictates the timing of sleep and wakefulness. Retinal light perception is the most powerful modulator of the circadian process, influencing not only the timing of sleep but also its internal architecture and consolidation through both acute alerting effects and chronic entrainment of the central clock (42).

The SCN orchestrates the timing of sleep through a network of efferent projections. One of the most critical pathways is a multisynaptic circuit to the pineal gland. The SCN projects to the paraventricular nucleus of the hypothalamus, which in turn sends signals down to preganglionic sympathetic neurons in the intermediolateral cell column of the spinal cord (43). These neurons drive postganglionic fibers from the superior cervical ganglion that innervate the pineal gland, controlling the synthesis and release of melatonin. During the day, the SCN is active and inhibits this pathway. At night, SCN activity wanes, disinhibiting the pathway and allowing for robust melatonin production. Light exposure at night, detected by retinal ipRGCs, rapidly reactivates the SCN, which clamps this pathway shut, acutely suppressing melatonin synthesis. The spectral sensitivity of this suppression reflex mirrors that of melanopsin, with short-wavelength blue light being the most potent stimulus (44).

In addition to its chronobiotic role, light exerts a direct and immediate alerting effect on the brain. This is mediated by ipRGC projections to key arousal centers, bypassing the SCN. These projections innervate the lateral hypothalamic area, home to the orexin/hypocretin neurons that are critical for maintaining consolidated wakefulness, as well as monoaminergic arousal centers in the brainstem, such as the noradrenergic locus coeruleus (45). Activation of these pathways by light can directly antagonize sleep-promoting signals. For example, the SCN also regulates the ventrolateral preoptic nucleus (VLPO), a key sleep-promoting center containing GABAergic and galaninergic neurons that inhibit arousal systems (46). The SCN promotes VLPO activity during the biological night. Light at night can therefore disrupt this balance, both by directly stimulating arousal centers and by suppressing the SCN's drive onto the VLPO, leading to fragmented sleep and increased awakenings (47).

The differential effect of light spectra on sleep is a direct consequence of the biophysics of retinal photoreceptors. Short-wavelength blue light (~480 nm), through its potent activation of the melanopsin system in ipRGCs, has the most significant effects on sleep regulation (11). Evening exposure to blue-enriched light has been demonstrated to not only suppress melatonin and delay sleep onset but also to alter subsequent sleep architecture, typically by reducing the amount of restorative slow-wave sleep, characterized by high-amplitude delta (0.5-4 Hz) electroencephalogram waves and decreasing the duration of rapid eye movement sleep (45). By contrast, evening exposure to long-wavelength red light, which minimally stimulates ipRGCs, has little to no effect on melatonin or circadian phase and preserves sleep architecture. This principle underpins the strategy of using 'circadian lighting' or blue-blocking filters to create a transition to sleep (44,48).

The clinical relevance of these mechanisms is most evident in individuals with disrupted retinal input. Patients with glaucoma or advanced diabetic retinopathy often suffer from severe sleep fragmentation and insomnia, which correlate with the degree of ipRGC damage as measured by objective tests such as the pupillary light reflex (49). In totally blind individuals without any light perception (that is, with complete optic nerve destruction or bilateral enucleation), the sleep-wake cycle often 'free-runs' with a period slightly longer than 24 h, leading to a condition known as non-24-h sleep-wake disorder (50). However, in blind individuals who retain functional ipRGCs, timed light administration can successfully entrain their rhythms, highlighting the therapeutic potential of targeting this residual NIF pathway. The integrity of the retinal photic input pathway is therefore a fundamental determinant of an individual's ability to maintain a stable and restorative sleep-wake cycle (12).

5. Systemic health consequences of retinal light perception

The influence of retinal light perception extends far beyond visual processing and sleep regulation, acting as the primary synchronizing agent for the entire organism's physiology. Through the RHT and other projections, photic information entrains the central SCN pacemaker, which in turn orchestrates a hierarchy of peripheral clocks in virtually every tissue (51). This establishes a direct and profound link between

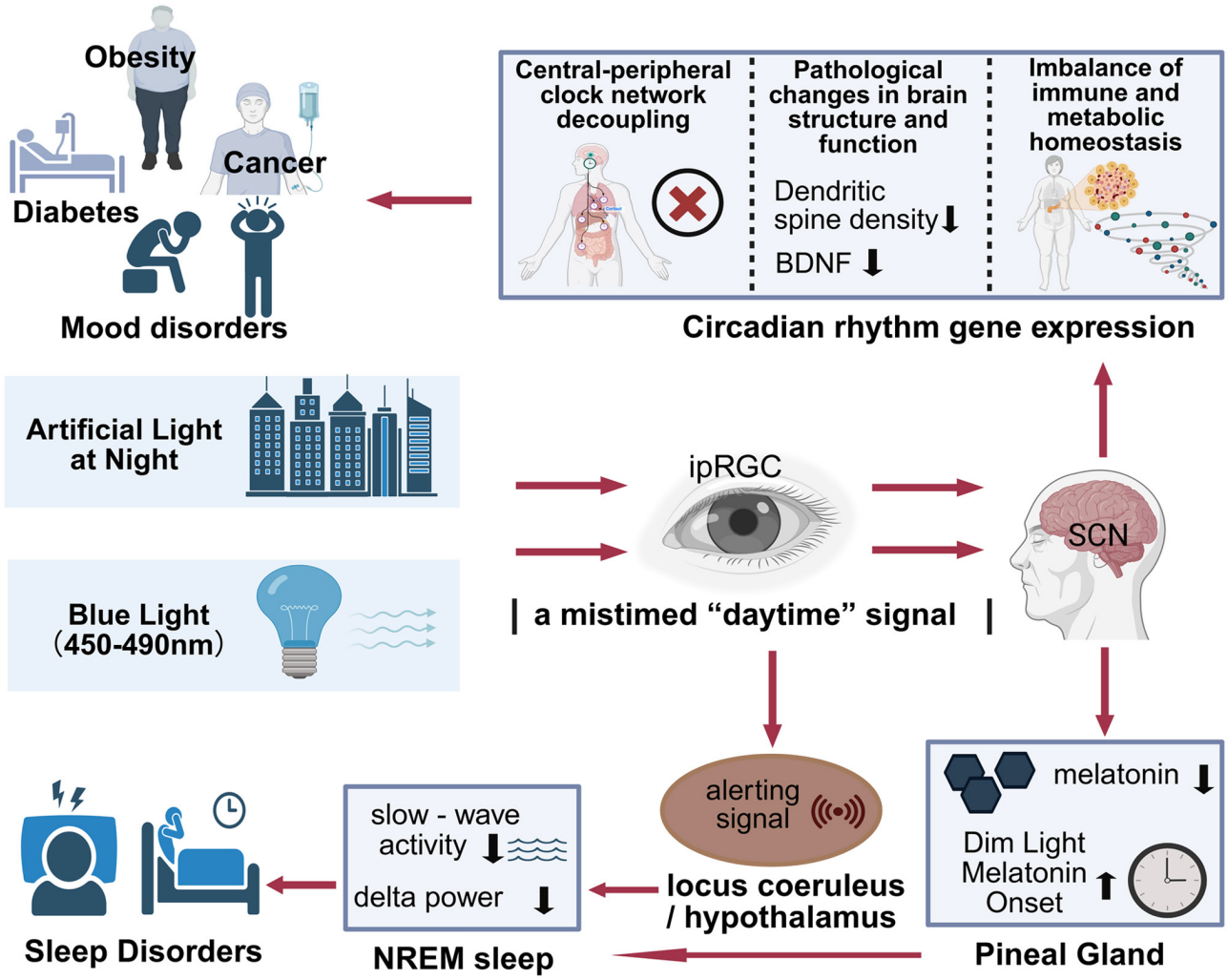

Figure 3. Retinal light input coordinates circadian rhythms and systemic health. Retinal light signals via the retinohypothalamic tract entrain the central circadian clock (SCN) to synchronize peripheral clocks and systemic physiology. Disrupted retinal signaling from disease or abnormal light causes circadian misalignment, affecting metabolism, cell cycle and immunity, contributing to chronic diseases. Direct retinal projections to non-circadian brain areas link light perception with mood and mental health. SCN, suprachiasmatic nucleus; ipRGCs, intrinsically photosensitive retinal ganglion cells; pCREB, phosphorylated cAMP response element-binding protein; BDNF, brain-derived neurotrophic factor; NREM, non-rapid eye movement.

ocular health, environmental light patterns and systemic well-being. Consequently, circadian disruption, initiated by aberrant retinal signaling from either pathological conditions or unnatural light exposure, is now understood as a fundamental pathogenic mechanism. It contributes to a spectrum of chronic diseases by desynchronizing the tightly regulated temporal expression of clock-controlled genes that govern metabolism, cell cycle and immune function. Furthermore, direct retinal projections to non-circadian brain centers inextricably link light perception to the neurobiology of mood and mental health (Fig. 3) (12).

Metabolic dysregulation and disease. The circadian system imposes a temporal order on metabolism, ensuring that anabolic and catabolic processes are aligned with feeding/fasting and activity/rest cycles. This coordination is achieved by the SCN synchronizing peripheral clocks within key metabolic organs. Chronic circadian disruption, epitomized by shift work or exposure to light-at-night, severs this synchrony, leading to internal temporal chaos with severe metabolic consequences (52).

In the liver, the local clock, driven by rhythmic transcription of Bmal1 and Clock, directly regulates hundreds of genes involved in glucose and lipid homeostasis. For instance, the clock-controlled protein REV-ERBα acts as a potent rhythmic repressor of key gluconeogenic genes, including glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, suppressing hepatic glucose output during the inactive/fasting phase (53,54). Simultaneously, the liver clock gates lipid metabolism by controlling the expression of sterol regulatory element-binding protein 1c and its downstream targets such as fatty acid synthase, restricting *de novo* lipogenesis to the active/feeding phase (55) Mistimed light exposure and consequent behavioral shifts (such as eating at night) create a conflict between the central SCN signal and metabolic substrate availability, uncoupling these genetic programs and leading to pathological states such as insulin resistance and non-alcoholic fatty liver disease due to incessant gluconeogenesis and lipogenesis (56,57).

In the pancreas, the clock within islet β-cells is critical for normal insulin function. BMAL1/CLOCK heterodimers directly regulate the transcription of genes essential for

every step of insulin secretion, from glucose transport (Slc2a2/GLUT2) and ATP production to the function of the ATP-sensitive potassium channels that trigger membrane depolarization. Circadian misalignment impairs glucose-stimulated insulin secretion and reduces insulin sensitivity in peripheral tissues, creating a direct pathway to the development of type 2 diabetes (58,59).

In adipose tissue, the local clock governs adipogenesis and lipid storage, partly through the rhythmic control of the master adipogenic transcription factor Pparg by BMAL1. This clock also controls the rhythmic secretion of key adipokines. The normal nocturnal peak of leptin, a satiety hormone, is blunted or shifted by mistimed light and sleep, disrupting hunger signals and contributing directly to obesity (60).

Circadian disruption and cancer pathogenesis. The link between circadian disruption and cancer is supported by robust epidemiological data and grounded in precise molecular mechanisms that couple the clock to cell proliferation and immune surveillance. The International Agency for Research on Cancer has classified shift work involving circadian disruption as a probable human carcinogen (3,61).

The core clock machinery is physically and functionally integrated with the cell cycle. Key clock proteins, such as period circadian protein homolog (PER)1 and PER2, can bind to and inhibit critical cell cycle promoters such as Cyclin D1 and the proto-oncogene c-Myc, acting as tumor suppressors. Conversely, BMAL1/CLOCK rhythmically regulate the expression of the cell cycle checkpoint kinase Wee1, which controls entry into mitosis. Circadian disruption dismantles this temporal gating, permitting uncontrolled cell proliferation (62).

A primary mechanistic link is the suppression of nocturnal melatonin by light at night. Melatonin is a potent oncostatic agent with pleiotropic anti-cancer effects. Through its receptors, MT1 and MT2, melatonin can inhibit signaling pathways crucial for cancer growth, such as the MAPK/ERK and PI3K/Akt pathways (63,64). It also has powerful receptor-independent functions as a free radical scavenger, protecting DNA from oxidative damage. Light-at-night exposure effectively removes this endogenous anti-cancer brake, a mechanism strongly implicated in the increased risk of hormone-sensitive cancers such as estrogen receptor-positive breast cancer and prostate cancer among night-shift workers (65).

Furthermore, the circadian clock regulates the body's anti-tumor immune response. The trafficking and cytotoxic function of immune cells, including natural killer (NK) cells and cytotoxic T lymphocytes, exhibit robust daily rhythms. For example, NK cell infiltration into tumors and their lytic activity are markedly higher during the early resting phase. Circadian disruption flattens these rhythms, leading to impaired immune surveillance and creating a permissive environment for tumor cells to evade detection and elimination (66).

Direct retinal pathways and mental health. The neurobiological connections between light and mental health are increasingly understood to be mediated by direct retinal projections to limbic and cortical circuits, independent of the SCN. Specific ipRGC subtypes, project to non-circadian centers that are fundamental to affective regulation (13). A critical pathway involves projections to the lateral habenula (LHb), a nucleus that encodes negative valence and aversive signals and is pathologically hyperactive in depression (67). The LHb exerts inhibitory control over midbrain monoaminergic systems, including the ventral tegmental area (VTA) for dopamine and the dorsal raphe nucleus (DRN) for serotonin. Preclinical studies show that acute light exposure can rapidly suppress the firing of LHb neurons via this retinal input, thereby disinhibiting VTA and DRN neurons. This provides a direct, fast-acting mechanism by which light can enhance motivation and elevate mood (5,68).

Another key target is the medial prefrontal cortex (mPFC), essential for executive function and the cognitive regulation of emotion. Light enhances activity and strengthens glutamatergic synaptic plasticity in the mPFC, probably via a multisynaptic ipRGC-thalamus-cortex pathway (69). This strengthens top-down control over subcortical structures such as the amygdala, which is involved in processing fear and anxiety.

The efficacy of bright light therapy for Seasonal Affective Disorder (SAD) is a clinical manifestation of these pathways. SAD is characterized by a phase-delayed circadian rhythm and a hypothesized 'retinal subsensitivity' to light (70). High-intensity light therapy acts as a potent retinal stimulus that both corrects the underlying circadian misalignment and directly modulates these mood-relevant circuits. The high comorbidity of depression in ophthalmic diseases such as glaucoma and retinitis pigmentosa is also explained by these mechanisms (71). The progressive loss of ipRGCs in these conditions severs the photic input to the SCN, LHb and mPFC, creating a state of 'biological darkness' that fosters a neurochemical and network-level state conducive to affective disorders, a pathology that transcends the psychological burden of vision loss (72). This suggests that therapies aimed at activating any residual ipRGC function could have significant mental health benefits even in low-vision patients.

Compromised adaptive capacity due to age and disease. The circadian system's ability to adapt to environmental changes, such as trans-meridian travel, depends on the robustness of the retinal signal relayed to the SCN. This adaptive capacity is markedly compromised by both normal aging and ocular disease. With aging, the crystalline lens naturally yellows, acting as a short-pass filter that blocks a significant portion of the blue light (460-480 nm) required to optimally stimulate melanopsin (73). This, combined with senile miosis (pupil constriction), dampens the photic signal reaching the retina, contributing to the flattened circadian amplitude, advanced sleep phase and fragmented sleep common in the elderly (11,74). Cataract surgery, by replacing the yellowed lens with a clear intraocular lens that transmits blue light, has been shown to robustly improve circadian entrainment and sleep consolidation, highlighting the clinical importance of retinal light hygiene. In glaucoma, the apoptotic loss of ipRGCs creates a permanent and progressive deficit in the NIF system, impairing the *gain* of the system's response to light and making it profoundly difficult for patients to entrain their rhythms or adapt to environmental changes (8,75).

6. The retina and the challenge of modern light exposure

The contemporary human light environment represents a dramatic departure from the evolutionary conditions under which our visual and circadian systems evolved. The transition from a natural regimen of bright, full-spectrum sunlight during the day and profound darkness at night to a life spent predominantly indoors under dim, spectrally-narrow electric light, coupled with pervasive exposure to artificial light at night (ALAN), presents a significant physiological challenge (76). The retina, as the first point of contact, is at the epicenter of this challenge and understanding its response to modern lighting is critical for public health (77).

The circadian potency of modern light sources. The advent and ubiquity of solid-state lighting, particularly 'white' light-emitting diodes (LEDs) and the back-lit screens of electronic devices have fundamentally altered the spectral diet of the modern eye. Unlike the smooth, black-body radiation curve of incandescent light, numerous white LEDs operate on a 'blue pump-yellow phosphor' principle (78). This creates a spectral power distribution (SPD) with a narrow, high-energy peak in the short-wavelength blue portion of the spectrum (typically 450-490 nm) to excite a phosphor that re-emits a broader band of longer-wavelength light. This blue peak aligns almost perfectly with the maximal spectral sensitivity of melanopsin in ipRGCs, making these sources a powerful, albeit often unintended, stimulus for the non-image-forming system (44).

When encountered in the evening, this blue-enriched light transmits a potent, mistimed 'daytime' signal to the SCN and other brain centers. The neurobiological consequences are quantifiable and significant. Exposure to typical indoor light levels can acutely suppress the amplitude and duration of the nocturnal melatonin profile and markedly delay its onset (the Dim Light Melatonin Onset, or DLMO), a key marker of circadian phase (79). This disruption directly affects sleep architecture by suppressing slow-wave activity and delta power during subsequent non-rapid eye movement sleep, a process vital for synaptic homeostasis and memory consolidation (80,81). The direct alerting effect, which counteracts homeostatic sleep pressure, is mediated by ipRGC projections to the noradrenergic locus coeruleus and the orexinergic neurons of the lateral hypothalamus. This highlights the inadequacy of traditional photometry, based on photopic lux, which is weighted towards cone sensitivity for vision (~555 nm) and fails to capture the biological potency of light (82). Consequently, the concept of α-opic lux, particularly Melanopic Equivalent Daylight Illuminance (MEDI), has emerged. MEDI quantifies light based on its activation potential for the melanopsin channel, providing a far more accurate metric for predicting circadian, neuroendocrine and alerting responses and it is becoming a critical tool for evidence-based lighting design (83).

Urban light pollution and chronic circadian disruption. Beyond personal devices, broad-scale urban light pollution constitutes a chronic and pervasive source of circadian disruption. ALAN from streetlights, buildings and advertising can infiltrate sleeping environments, creating nocturnal light levels that, while seemingly low (often ranging from <1 to >10 lux), are well within the activation threshold of the highly sensitive ipRGC system, especially when integrated over a number of hours (84). Large-scale epidemiological studies, leveraging satellite data to quantify outdoor ALAN, have found strong correlations between residence in brightly lit areas and increased odds ratios for obesity, type 2 diabetes, mood disorders and certain cancers (85-87).

Causal mechanisms have been elucidated in controlled animal models. Chronic exposure to dim light at night (~5 lux) is sufficient to markedly dampen the amplitude of the SCN's rhythmic molecular clock gene expression. This central disruption cascades to peripheral systems and directly impacts brain structures crucial for mood and cognition (88). For example, in rodents, dim ALAN has been shown to reduce dendritic spine density in the CA1 region of the hippocampus, decrease levels of brain-derived neurotrophic factor and impair performance on hippocampus-dependent spatial memory tasks such as the Morris water maze (48). These structural and functional deficits are the neurobiological underpinnings of the depressive-such as behaviors, such as increased immobility in the forced swim test, observed in these animals. The retina's ipRGCs are the unequivocal mediators of this effect, transmitting a persistent, low-level disruptive signal to the brain throughout the biological night (44).

Ophthalmic and behavioral intervention strategies. In response to these challenges, several intervention strategies based on the neurophysiology of the NIF system have been developed. Blue-light filtering lenses aim to attenuate the evening circadian stimulus (89). These range from lenses with blue-reflecting coatings to short-wavelength-absorbing filters (which appear yellow or amber). Studies show that amber lenses, which markedly block light below ~500 nm, can effectively prevent light-induced melatonin suppression and preserve the natural timing of the DLMO (90). However, the clinical efficacy remains debated, as it is highly dependent on the precise spectral characteristics and the total amount of light being blocked. Furthermore, indiscriminate use during the day could be counterproductive, dampening the necessary alerting and entraining signals (91).

A more proactive approach is structured light therapy, which uses the light Phase Response Curve as a guiding principle. Morning bright light therapy (typically 10,000 photopic lux, which is high in melanopic content, for 30 min upon awakening) is a first-line treatment for SAD and delayed sleep-wake phase disorder because it provides a powerful, timed phase-advancing signal to the SCN (92). For patients with retinal diseases, these protocols can be personalized. For instance, in a patient with retinitis pigmentosa who has lost cone function but retains ipRGCs, a therapeutic device could use monochromatic blue light (~480 nm) to selectively and efficiently activate the residual melanopsin system for entrainment, a wavelength that would be useless for image formation (43).

The future of lighting lies in dynamic, human-centric (or integrative) lighting systems. These systems use multi-channel LED engines (such as combining red, green, blue and white/amber LEDs) to actively sculpt the SPD of indoor light throughout the day (93). The goal is to create a biomimetic light cycle: high-intensity, high-CCT (Correlated Color

Table II. Effect of ophthalmic diseases and modern lighting on NIF functions and intervention strategies.

Condition/Factor	NIF system deficit	Main symptoms	Potential intervention
Glaucoma	ipRGC loss, reduced RHT signaling	Sleep disturbance, mood disorders	IOP control, structured light therapy, pupil response tests
Retinitis pigmentosa	Loss of rods/cones, ipRGC preserved	Poor circadian entrainment, insomnia	Blue-light therapy, time-restricted lighting
Aging/cataract	Reduced blue light transmission	Advanced sleep phase, fragmented sleep	Cataract surgery, daylight exposure
Urban ALAN (light pollution)	Excess blue light at night	Circadian misalignment, metabolic risk	Blue-blocking filters, smart home lighting
Shift work	Chronic circadian disruption	Insomnia, metabolic disease, cancer	Scheduled light/dark exposure, chronotherapy

NIF, non-image-forming; ipRGCs, intrinsically photosensitive retinal ganglion cells; RHT, retinohypothalamic tract; IOP, intraocular pressure; ALAN, artificial light at night.

Temperature) light with a high MEDI (>250 melanopic lux) in the morning and midday to maximize alertness, performance and circadian entrainment; followed by a gradual transition to low-intensity, low-CCT light with a markedly reduced MEDI (<10 melanopic lux) in the evening, thereby creating a state of 'circadian darkness' that protects the melatonin rhythm and facilitates sleep (37,94). A summary of clinical conditions, their NIF deficits and possible interventions is provided in Table II.

7. Future research directions and unanswered questions

Despite monumental progress in understanding the retina's role in NIF functions, numerous critical questions and technological challenges remain. Future research must pursue a multi-pronged approach, combining molecular genetics, systems neuroscience and clinical investigation to further unravel the complexities of retinal light perception and translate this knowledge into effective clinical and public health strategies (95).

A primary frontier is the deeper molecular and functional characterization of ipRGC diversity. While the M1-M6 classification has provided a valuable framework, it is probably an oversimplification. Single-cell RNA sequencing and spatial transcriptomics are poised to reveal a more granular taxonomy of ipRGC subtypes, identifying unique molecular signatures, developmental lineages and signaling pathways for each (96). A key goal is to precisely map the full 'projectome' of each subtype, that is, to identify all of its downstream brain targets, and to functionally interrogate the role of each specific projection in behavior and physiology using advanced techniques such as optogenetics and chemogenetics in animal models. Understanding the differential vulnerability of these specific subtypes in diseases such as glaucoma is a critical clinical question that could lead to more targeted diagnostics and neuroprotective strategies. Furthermore, the detailed biophysical properties of melanopsin itself, including its signaling dynamics and regeneration cycle under various lighting conditions and in pathological states, warrant continued investigation (97).

The development of personalized light therapy and precision light exposure management represents a significant translational goal (98). The current 'one-size-fits-all' approach to light therapy does not account for the vast inter-individual variability in light sensitivity, chronotype, genetics (such as polymorphisms in clock genes), age, or the health status of the retina. Future research should focus on developing objective biomarkers, perhaps based on pupillometry, melatonin profiles, or electroretinography, to quantify an individual's NIF function. These data could then be integrated with genetic information and lifestyle monitoring from wearable sensors into machine learning algorithms to generate truly personalized light 'prescriptions' (99). This would involve specifying the optimal dose (intensity), spectrum, timing and duration of light needed to achieve a desired therapeutic outcome, whether it be advancing a delayed sleep phase, alleviating depressive symptoms, or bolstering circadian rhythms in an elderly individual or a patient with retinal disease. The integration of such intelligent systems with smart home and workplace lighting environments could enable the seamless, automated delivery of optimal light exposure throughout the 24-h day (100).

Finally, progress in this field will be critically dependent on enhanced interdisciplinary collaboration. The study of retinal light perception sits at the crossroads of ophthalmology, neuroscience, sleep medicine, psychiatry and engineering. Large-scale, longitudinal studies are needed to move beyond correlation and establish causality between specific light exposure patterns and long-term health outcomes, such as the incidence of metabolic disease or cognitive decline. Collaboration between ophthalmologists and neuroscientists is essential for elucidating the precise circuit-level mechanisms by which retinal diseases lead to systemic symptoms and for co-developing novel therapies that target the NIF system (101). Similarly, partnerships with sleep physicians and psychiatrists will be crucial for designing and implementing rigorous clinical trials to expand the application of light therapy to a broader range of disorders and to optimize its combination with pharmacological or psychological treatments (102). By integrating multi-modal data from genomics, neuroimaging and wearable physiological sensors into

comprehensive computational models, the scientific community can hope to build a holistic, systems-level understanding of how light, as perceived by the eye, shapes human health and well-being (80).

8. Conclusion

The retina's functional scope extends far beyond its role as an organ of sight; it is a critical neuroendocrine gateway that translates environmental light into the fundamental language of biological time. Retinal dysfunction, whether caused by disease or injury, not only leads to visual impairment but is frequently accompanied by a debilitating constellation of non-image-forming deficits, including circadian arrhythmia and sleep disorders, which underscores the imperative of maintaining retinal health for systemic physiological stability. Concurrently, the unprecedented light exposure patterns of modern life, dominated by indoor living and nocturnal blue-light exposure, pose a continuous challenge to the retina's photosensory mechanisms, exacerbating the risk of circadian misalignment. The confluence of these pathological and environmental factors profoundly affects the retina's ability to regulate circadian rhythms and sleep, highlighting the pressing need for scientifically-guided strategies to manage light exposure and preserve retinal function. A deep and mechanistic understanding of retinal photobiology, particularly the function of the melanopsin-ipRGC system, provides a robust foundation for designing precise and personalized light-based interventions (103). A clearer appreciation of the NO-cGMP pathway in the SCN, alongside melanopsin-driven glutamatergic and PACAP signaling, may refine light-based interventions and improve interpretation of circadian vulnerability in ophthalmic disease. Advanced light therapies and intelligent lighting technologies hold immense promise for improving sleep quality, stabilizing mood and preventing a host of rhythm-related pathologies. The continued synergy of ophthalmology, neuroscience and sleep medicine will drive further discovery, fostering the development of novel diagnostic and therapeutic paradigms that leverage the power of light to optimize human health.

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Authors' contributions

MY conceived the study, conducted the literature search, drafted the manuscript and designed the figures. HL contributed to literature screening, data extraction and verification, literature review and critical manuscript revision. RZ participated in the literature search, manuscript drafting and data analysis. YL collected literature, prepared tables and revised the manuscript. SS supervised the overall project, was responsible for manuscript writing and critical revision. AY supervised the study and revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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