What happens when circadian rhythms go wrong, and why we should care

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First submitted: *September 15, 2023*
Revision accepted: *October 28, 2023*
Revision submitted: *October 26, 2023*
Published: *December 2023*

Peer reviewed

Introduction

The circadian clock is a complex, evolutionarily conserved system that exists across multiple levels in almost every organism on Earth. The normal function of this circadian system relies on perfect synchrony across cells and tissues. When this is threatened, the clock contributes to the pathophysiology of a vast range of diseases, including diabetes, neurological disorders, and cancer. Modern lifestyles have created many obstacles to normal circadian function, ranging from pervasive changes, such as decreased daytime light exposure and increased nighttime artificial light exposure, to more extreme changes, such as chronic jet lag due to shift work. A constant minor desynchrony even arises from the difference between an individual's internal circadian clock and the external day, as the internal circadian period likely deviates from the 24-hour external period depending on factors such as age and genetics. Although it is difficult to study human circadian rhythms and the consequences of disrupting them, epidemiological and animal models suggest that the disruption of the circadian system has profound health consequences. In addition to being vulnerable to these effects, the eyes also play a crucial role in the circadian system, so any threats to the eye may have effects that extend well beyond the eye itself.

What are circadian rhythms?

The circadian system

Imagine the crescendo of an orchestra, with each musician contributing a unique melody that blends into one cohesive symphony. The orchestra is the analogy most often used to describe the circadian system—the natural timekeeper shared by almost every organism on Earth in some form. The conductor in this analogy is a small group of cells in the hypothalamus called the suprachiasmatic nucleus, or, more commonly, the master clock. Instead of gestures of the baton, the signals of this conductor are hormonal and neuronal, sent around the body to anticipate the timing of our environment. Almost every tissue in the body possesses its own circadian clock capable of a distinct rhythm but harmonized by the master clock, at least in healthy individuals. Distinct circadian clocks are also found in various components of the eye, including the retina. However, the neural retina is special among these peripheral clocks since it is not under the control of the master clock. Referring again to the orchestra analogy, it merits a special role, perhaps as the score that the conductor consults to lead the rest. This is because the most important timing signal of the circadian system is light, which is detected and interpreted by the retina before it is transmitted to the master clock via a specialized tract that directly links the retina

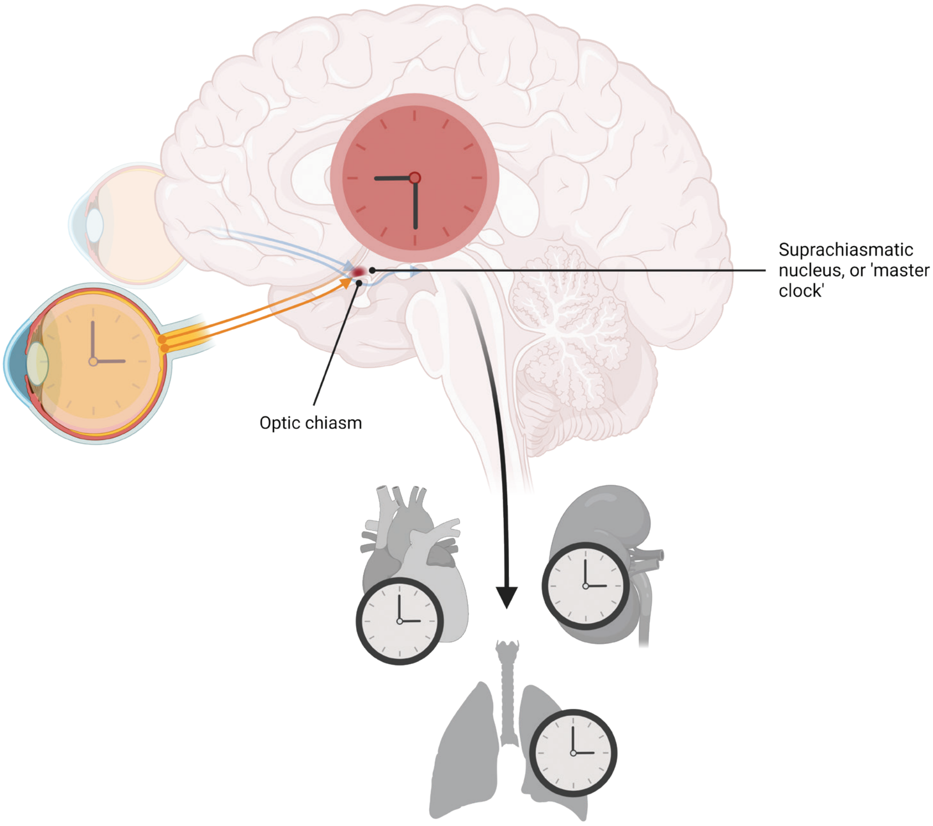

Figure 1. The circadian system is led by a master clock in the brain called the suprachiasmatic nucleus. This master clock, a bilateral structure in the anterior hypothalamus, uses both neuronal and hormonal signals to keep peripheral tissue clocks around the body in time with the external day. While the retina also has a tissue clock, it holds a special place in this system. Instead of taking timing cues from the master clock, it provides the master clock with the light information through the retinohypothalamic tract that it uses to tell time. This means that any threats to the eye have the potential to impact the timing of the entire body. Created with BioRender.com.

to the master clock (**Figure 1**).

The centrality of the retina to the circadian system is exemplified by the position of the suprachiasmatic nucleus, which is nestled directly above the optic chiasm. It is here that a specialized tract from the retina diverges from the visual processing neurons to feed direct light information to the master clock. This tract, the retinohypothalamic tract, is comprised of specialized retinal cells that facilitate body timing. These are a third class of relatively recently discovered photosensitive cells in the eye, the intrinsically photosensitive retinal ganglion cells, so called because of their possession of the photopigment melanopsin. These cells make up less than 1.5% of ganglion cells and have roles ranging from circadian timing to the pupillary light reflex and sleep timing.[1]

The molecular circadian clock

The smallest level of the circadian system is the molecular clock, an intricate network of proteins that regulate each other to create a feedback loop. In this loop, clock genes produce proteins that inhibit their own activity in a daily pattern, creating a rhythmic oscillation that cycles once every 24 hours. The relevance of this clock stems from not only how the clock genes interact with each other but also how they directly control the expression of thousands of other genes to drive rhythmic gene expression, metabolic activities, and other processes in the cell. Somewhere between 10 and 15% of all gene transcription is rhythmic, and as many as 50% of mammalian genes are predicted to be rhythmically expressed in at least one tissue.[2] The eye is no exception to this; as many as 9% of genes are expressed rhythmically in the retina.[3] Circadian rhythms exert a profound impact on visual function and eye health, influencing genes associated with angiogenesis,[4] inflammation,[5] and responses to hypoxia,[6] among others.

The importance of circadian rhythms for overall health

Due to its multiple levels of organization and because all circadian clocks take cues from the environment, including not only light but also feeding and activity, the circadian system is susceptible to disruption at many levels. This disruption can occur in the relationship between the master and peripheral clocks, the relationship between the cells within a clock, or even between the clock and the external environment. Circadian disruption refers to a disturbance or interruption of the body's natural circadian rhythm, with serious consequences. A well-aligned circadian rhythm promotes restorative sleep, improves cognitive function, enhances mood, and supports optimal metabolism. It also optimizes the timing of digestion, nutrient absorption, and detoxification processes. As such, circadian disruptions, including those caused by shift work, jet lag, or excessive exposure to artificial light at night, can lead to misalignment, which has been associated with an increased risk of various health issues, including sleep disorders, obesity, diabetes, cardiovascular disease, and even certain types of cancer. Notably, the World Health Organization classified circadian disruption as a probable carcinogen in 2007.

Are circadian rhythms important for healthy eyes?

The rhythmic nature of the eye, especially the retina, may not come as a surprise, considering that the eye's purpose is to accommodate vision across light changes that span many folds of magnitude every day, from starlight to midday sun. These same light changes preoccupy the circadian system in its quest to correctly orientate us with the timing of our environment. Some rhythms in the eye come from the light itself, but of the 2,670 genes in the retina that have a rhythmic pattern of expression, around 2,400 are under the control of the genes that make up the circadian clock.[7] Circadian rhythms in the eye are responsible for many aspects of vision, including visual acuity, contrast sensitivity, color vision, and adaptation to darkness. To make this happen, many fundamental processes in the eye are under the control of the circadian clock, like photoreceptor disc shedding,[8] melatonin and dopamine action,[9] and electrical responses to light.[10]

The circadian clock in the retina is more complicated than some clocks in other organs of the body. It might be more accurately described as a collection of clocks since the various layers and cells of the retina possess their own rhythms in clock gene expression.[11,12] Because of this complexity, when the clock gene expression of the whole retina was initially measured together, distinct rhythms blended to give the impression of an unrhythmic tissue. We now appreciate that the retina is instead complexly rhythmic, with synaptic connections and electrical communication between the layers of the retinal clock giving rise to daily morphological and biochemical changes that researchers are still characterizing. Each layer contains cells

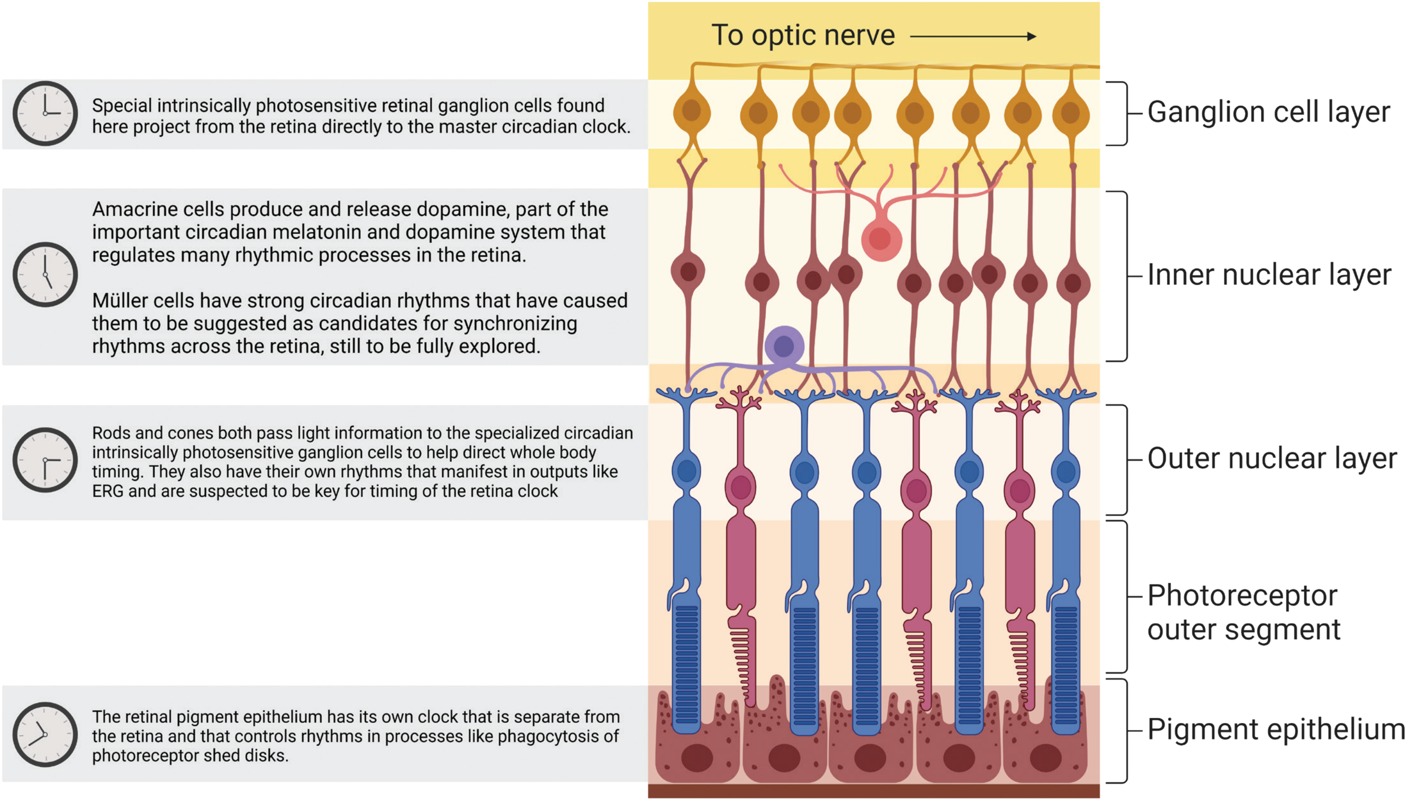

Figure 2. Each layer of the retina plays a role in generating circadian rhythms either for the retina itself or for the circadian system as a whole. Within each of these layers, different cell groups express clock genes and proteins that serve to optimize cellular physiology and contribute to either timing in the retina or timing of the wider circadian system. More is known about how the retina directs the timing of the master clock than how it regulates itself, but some of the key players in the retinal circadian clock are the photoreceptors, Müller glial cells, and amacrine cells. Created with BioRender.com.

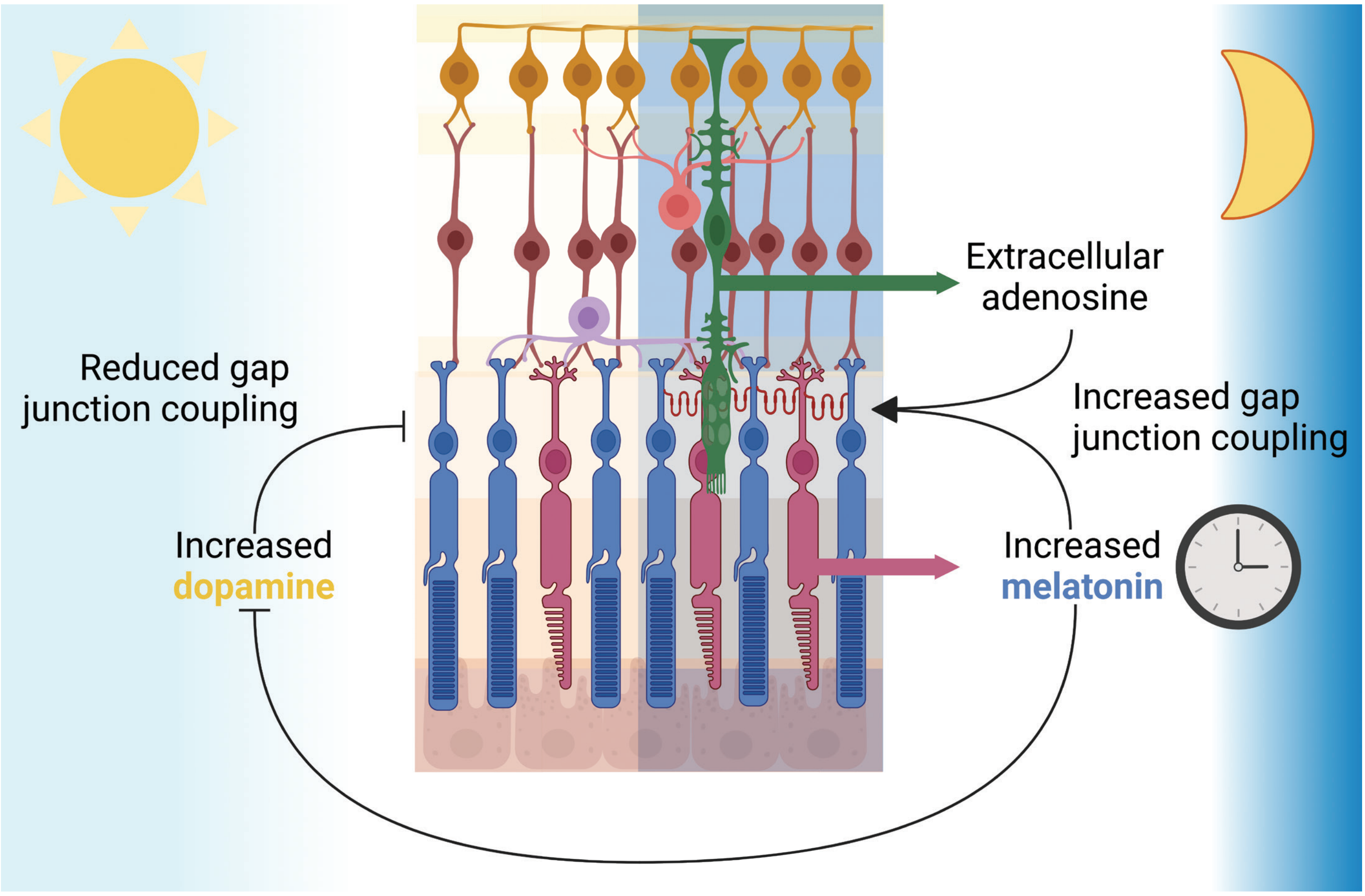

Figure 3. Driven by the circadian clock, melatonin levels increase in the dark and decrease in the light; dopamine levels follow the opposite pattern, whereas extracellular adenosine increases at night. In these two clock systems, the inverse relationship between melatonin and dopamine and the changes in adenosine levels are important for maintaining the normal function of the eye. Each plays many roles in the retina, but one circadian function is the changing level of connectivity between rod and cone photoreceptors. More gap junction coupling at night enables better vision in dim lighting conditions, whereas during the day, cone-mediated vision with high spatial accuracy is prioritized. Created with BioRender.com.

that are important for either the circadian rhythms of the entire circadian system or the rhythms in the retina itself (**Figure 2**). The full control of the retinal clock is yet to be fully elucidated, but several cell groups, including the photoreceptors, have been implicated, and most cells, including glial cells,[13] contain a circadian clock.

The earliest purpose of circadian rhythms in the eye is to shape normal development, although less is known about the role of the circadian clock in development in general. We know that the circadian clock guides the timing of cell division as the retina develops and that suboptimal timing can impact cell fate, leading to too many or too few different cell groups.[14] If the circadian clock is lost in these developing cells, changes occur when the cells exit the cell cycle, and this leads to changes in the final numbers of neuronal cells, such as retinal ganglion and amacrine cells,[14,15] and in the spectral identity of cone photoreceptor cells.[16]

Taking rhythms into account in practice

In the developed eye, the role of the clock changes to protection and homeostasis. Intense light damage to photoreceptors, for example, is twice as bad at night as it is during the day.[17] Circadian rhythms also continue to control diverse functions. This can be seen in some techniques that we use to monitor the eye, such as the electroretinogram (ERG). The electrical response of the retina to light is under circadian control, and this can be seen in the ERG response depending on the time of day that it is recorded.[10,18] For example, the cone ERG response in mice peaks at dawn and dusk, which makes sense from an evolutionary perspective in nocturnal animals that seek food at these times.[10] This rhythm was originally thought to be driven by cone photoreceptor cells. More recently, research has shown that changes in the ERG response from day to night arise from regulation by rod cells, specifically the control of electrical coupling between rods and cones.[19] This rhythm facilitates a boosted response in dimmer lighting, with the circadian clock anticipating light changes to optimize vision from day to night. Daily changes in gap junction coupling between rods and cones have been attributed to both extracellular adenosine levels and the melatonin and dopamine cycle, all of which are under circadian control[20,21] (**Figure 3**).

The daily pattern and interactions of melatonin and dopamine have been implicated in many rhythmic processes in the eye and in many disease processes. Melatonin, which is strongly associated with sleep, is a hormone primarily produced by the pineal gland in the brain, but it is also produced in the retina. Its release is under circadian control in the retina, and the nature of this release was first used to prove that the retina has its own endogenous circadian clock, namely that it followed a circadian pattern that continued even in darkness but was entrained by light.[22] Dopamine is a neurotransmitter found in both the brain and the retina. Melatonin and dopamine interact to represent a duality of function. Melatonin in particular has been implicated in various eye diseases because of its role in regulating circadian rhythms and protecting against oxidative stress.

Like the ERG response, intraocular pressure (IOP) also fluctuates throughout the day under circadian regulation through the management of the balance of aqueous humor production and drainage.[23] Several studies have revealed rhythmic fluctuations in IOP, with peak levels often observed during the early hours of the day.[24,25] This circadian regulation occurs through direct neural control via sympathetic innervation and hormonal control,[23] specifically by melatonin.[26] Glaucoma, a leading cause of irreversible blindness worldwide, is characterized by progressive damage to the optic nerve, which is often associated with increased IOP. Acknowledging IOP rhythms

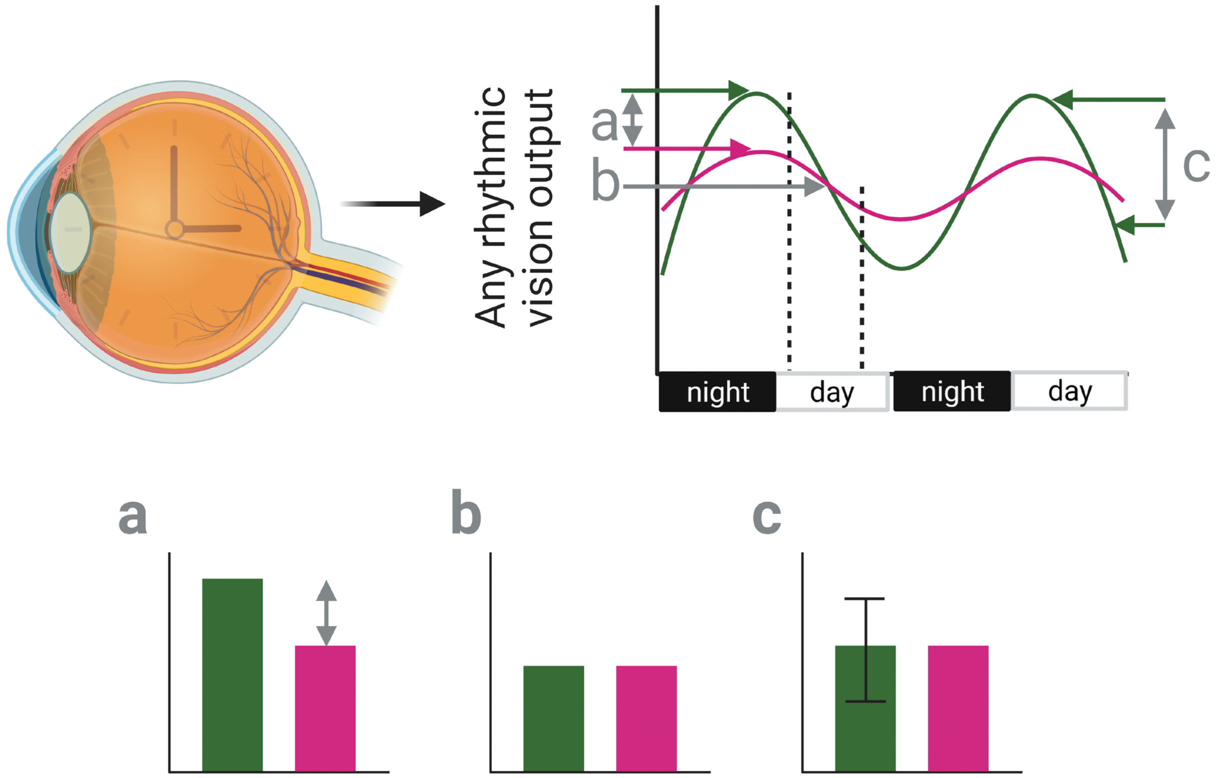

Figure 4. Circadian control in the eye means that many outputs can change from day to night. Examples of rhythmic outputs include the electroretinogram-measured retinal response to light and intraocular pressure. When any biological process is under circadian regulation, or, in the case of the eye, regulated by light, the timing of the measurement influences the output. Moreover, in research, a disease might not significantly change an output at a specific time but may instead change the rhythm, leading to a pathology that is undetected because of the time of sampling. Choosing the right time of day to record a rhythmic output carefully might (a) reveal differences, whereas choosing the wrong time (b) could disguise them. It is also important to consider that (c) comparing measurements taken at different times will result in undesirable variance in experimental groups. Created with BioRender.com.

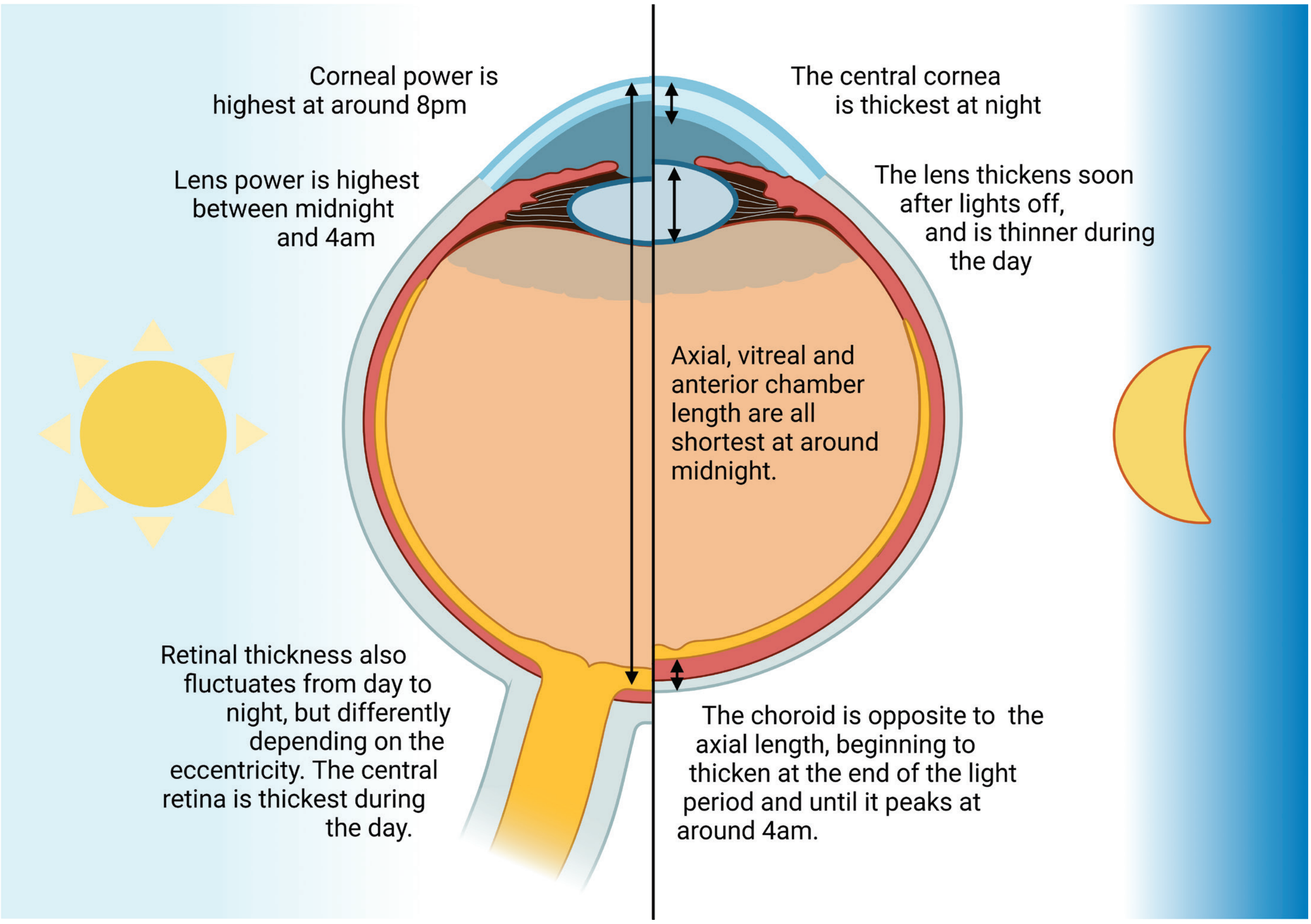

Figure 5. Many dimensions of the eye change from day to night and are driven by several different mechanisms, including an influx of water into the cornea while the eyelid is closed during sleep. *Some changes in the rhythms of different measurements have been reported in individuals with myopia, including a higher amplitude rhythm in axial length across the day and less change in choroid thickness. Understanding these rhythms in the growing eye might provide insight into the development of myopia. Created with BioRender.com.*

is valuable in the development of glaucoma therapies; for example, these rhythms are important when considering the timing of medication administration to target the peak IOP and optimize treatment efficacy. This is part of why some treatments, such as prostaglandin analogs, are recommended for use in the evening, whereas β-blockers, which do not have a 24-hour effect, are taken in the morning when they might coincide with the expected peak in IOP. Considering rhythms when advising patients is complicated by the individual variations in all rhythms, including in IOP, and by the further effects of multiple treatments on rhythms.[27] For example, multiple eye drops have been shown to flatten IOP variation. In practice, patient adherence must also be considered, and better adherence to morning administration of once-daily treatments is well-evidenced.[28] Glaucoma and IOP changes are also associated with retinal vein occlusion; although circadian rhythms have not yet been directly associated with this pathology, it is interesting to note that the incidence of macular ischemia is elevated in patients who lack normal circadian rhythms in systemic blood pressure, specifically those who lack a dipping pattern in nocturnal blood pressure.[29] Together, these observations point to a crucial role of the circadian system in fine-tuning the timing of pressure changes in the eye and a wider system that merits further study. These examples of circadian-regulated measurement outputs of the eye also raise another point for consideration in healthcare and research. Rhythms and timing should both be considered when evaluating measurements to provide a clearer picture of what is happening with an individual patient or with a whole patient cohort (**Figure 4**).

Disrupted eye rhythms and disease

Many aspects of modern life threaten circadian rhythms, most of which relate to light and thus affect the retinal clock as well. Prolonged nighttime exposure to artificial light, particularly the blue light emitted by digital devices and indoor lighting, interferes with the circadian system and leads to irregular sleep patterns and reduced sleep duration. This not only has an immediate and direct effect on the eye by harming the eye's regenerative and repair processes during rest, but these modern circadian disruptions also have long-term impacts on many aspects of eye health. Preclinical studies have linked circadian disruption to a range of pathologies of the eye, including age-related macular degeneration (AMD),[30] glaucoma,[31] and diabetic retinopathy.[32] Circadian disruption has even been linked to myopia, with the rising prevalence of the circadian challenges listed above providing a convenient explanation for the rapidly growing but geographically uneven occurrence of the condition. Many ocular dimensions vary daily,[33] (**Figure 5**) and removing the circadian clock from the eye in experimental animal models induces myopia similar to that seen in humans.[34]

How does circadian disruption affect eye health?

When circadian challenges, including shift work and early or late behavior tendencies, are replicated in otherwise healthy animal models, worrying changes such as decreased metabolic efficiency and disrupted cardiac

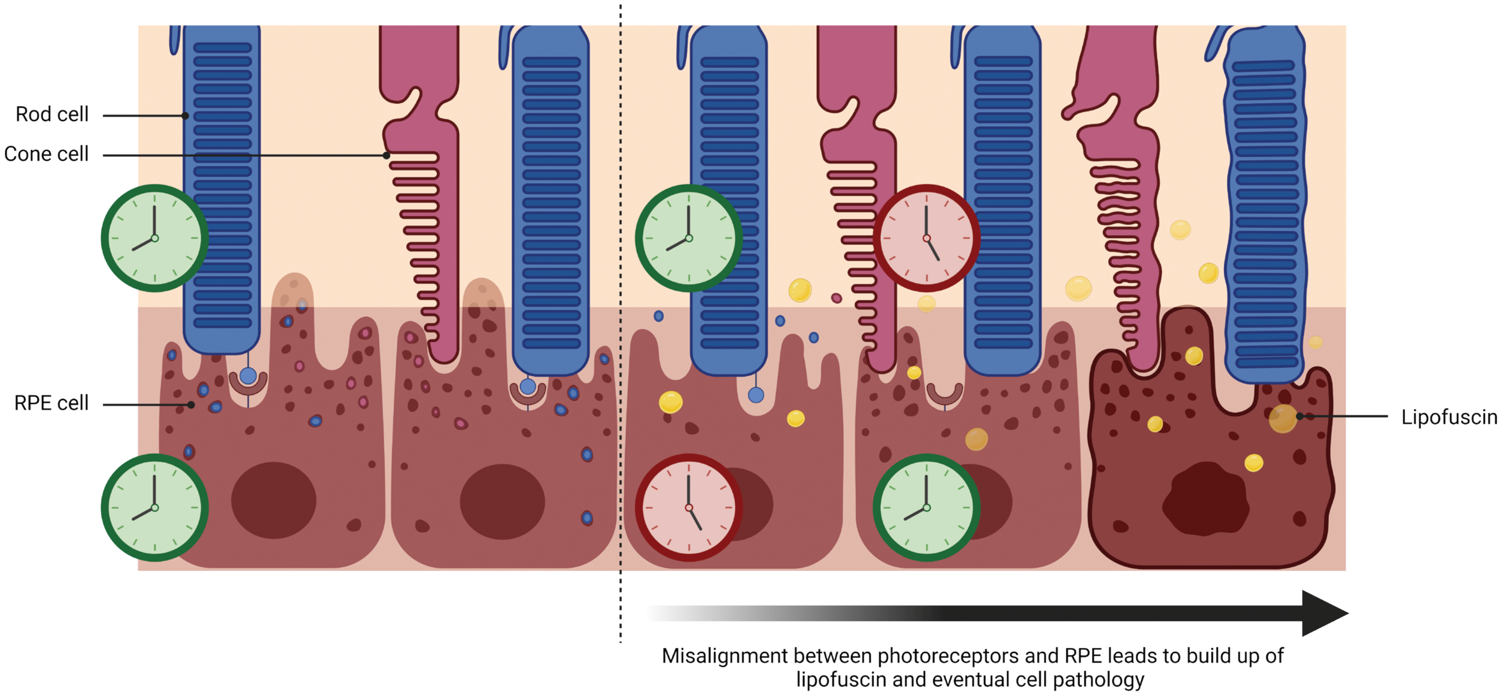

Figure 6. Misalignment between the retinal pigment epithelium (RPE)-driven phagocytosis peak and photoreceptor disc shedding is one hypothesis as to why photoreceptors seem to be particularly affected in animal models of circadian misalignment. *Studies have shown that even a three-hour shift in the timing of the RPE phagocytosis peak can drive a buildup of lipofuscin in the RPE and eventually a loss of RPE and photoreceptor cells.[43] Created with BioRender.com.*

function result.[35] Considering the extent of circadian rhythmicity in the eye, it stands to reason that the eye also suffers when daily rhythms are disturbed. Indeed, visual acuity, retinal thinning, and photoreceptor decreases are observed in mice when their circadian rhythms are disrupted.[36] The mechanisms at play in these models are still under investigation, but one hypothesis to explain harm to photoreceptors in particular is a potential timing conflict between the neuroretinal clock and the retinal pigment epithelium (RPE), the photoreceptor's closest neighbors in the eye. This hypothesis is based on the fact that the neuroretinal clock sets its time independently from the central body time. The RPE also has a clock that dictates the rhythms of many of its functions, including some that are crucial to the health of the photoreceptors. One such function is the clearing away of debris shed by the photoreceptors every day as part of their normal cycle. However, the RPE clock is controlled separately from the clock in the rest of the retina. In situations in which an individual's body timing does not correspond to their external light cycle, misalignment between these two clocks might occur.

The clock in the retina is entrained by light, with either the light itself or the resulting circadian rhythms dictating the daily timing of a wide range of processes. This is not true for the RPE,[37,38] which takes its timing cues from elsewhere, including melatonin levels. This raises the possibility that these two tissues could stop working harmoniously. One of many crucial jobs of the RPE is to phagocytose the photoreceptor's outer segments, which are shed normally every day, thus preventing photoreceptor degeneration due to a buildup of harmful materials.[8] This phagocytosis is circadian-controlled, with most happening around two hours after light onset to coincide with when the rods shed the most.[39,40] We know that this phagocytosis is important for general health, but the presence of a rhythmic pattern with a peak at the right time is key for the health of both the RPE and the photoreceptors.[41,42] Even a small shift in the timing of the phagocytosis peak can lead to photoreceptor pathology[43] (**Figure 6**). It is not yet clear how this rhythm, or the synchronization between the RPE and retina, is achieved, but like the retina, the RPE possesses its own circadian clock. In normal disc shedding, early morning rod shedding precedes a burst of RPE phagocytosis to rapidly clear the shed debris. Rod cells even exhibit a conserved phosphatidylserine domain, which signals for phagocytosis upon light onset.[44] These two pieces of evidence might suggest photoreceptor control; however, the peak in this 'eat me' signal is lost in mice without RPE rhythms.[42] Moreover, the genetic silencing of the clock in the RPE but not in the retina abolishes daily rhythms of phagocytosis.[45]

An example in disease: diabetic retinopathy

Diabetic retinopathy is one of the most common threats to vision, and its prevalence is increasing worldwide; therefore, it continues to be a subject of great focus in research and treatment development. The occurrence of circadian disruption in diabetes is now widely acknowledged, as is the appreciation that circadian disruption might play a role in the rapid rise of the disease, particularly for type 2 diabetes. The role of disruption in diabetic retinopathy is of growing interest. Many normal eye rhythms have already been observed to be disrupted in diabetic retinopathy, including retinal thickness,[46] pupillary diameter,[47,48] melatonin level,[47,49] and metabolic function.[3,50]

Interestingly, several of the treatments currently used or under investigation for diabetes target circadian rhythms. Melatonin, already mentioned several times, is one. Another treatment of note is metformin, which activates positive modulators of the molecular circadian clock[51] and changes the expression of the clock genes. These observations led to testing of the effects of metformin in the eye in animal models of type 2 diabetes, in which the drug upregulated an enzyme involved in melatonin production and melanopsin, the circadian photopigment produced by the intrinsically photosensitive retinal ganglion cells.[52] Conversely, panretinal photocoagulation, the first-line therapy for proliferative diabetic retinopathy, may exacerbate circadian disruption. This has been suggested because abnormal fluctuations of cortisol (in this case used as a marker of circadian disruption) have been reported in laser-treated patients,[53] possibly as a result of damage to the retinal ganglion cells; this topic requires further studies.

Angiogenesis, the formation of new blood vessels and a key process in many disease courses, is intricately linked to circadian rhythms in both development and disease. Studies have shown that the expression of genes involved in angiogenesis, such as vascular endothelial growth factor (VEGF), exhibits a circadian rhythm in the retina and RPE.[4,26] Moreover, circadian disruption has been shown to impair angiogenesis in the retina, and rhythmic environmental light is needed for normal vessel density.[54] The disruption of circadian rhythms may contribute to retinal diseases that involve angiogenesis, such as diabetic retinopathy and AMD.

The growing evidence that AMD is linked to circadian disruption is supported by many observations in experimental models. Without circadian rhythms in the eye, mice show a greater decline in photoreceptors as they age and faster deterioration of cone cell viability and function, like that observed in aging.[55] Together, these observations have even precipitated calls for the development of a 'chronoprotective system' at a recent meeting of experts,[56] possibly centered around the use of melatonin. Circadian rhythms are known to weaken and become dysregulated with age, and these changes are likely to contribute to and have been associated with age-related eye disease.[57]

Conclusion

In conclusion, the profound influence of circadian rhythms on eye health cannot be overstated. The maintenance of healthy sleep–wake cycles is paramount to the well-being of the eyes, and disruptions to these rhythms can contribute to a range of ocular conditions and threaten normal visual function. Recognizing the critical connection between internal clocks and eye health and public awareness of the importance of circadian rhythms are crucial, along with the support of ongoing studies and advancements in circadian rhythm research. Appreciating circadian rhythms creates opportunities to optimize treatment delivery, enhance precision medicine applications, and improve the reproducibility of the measurements we take, both in the clinic and the lab. Examining the circadian clock might also unveil new disease mechanisms that affect the rhythm if it is not balanced at any single time of day, possibly providing novel therapeutic targets. By understanding the intricate connection between circadian rhythms and the eye, we can develop strategies to mitigate the adverse impact of circadian disruption on eye health and promote ocular well-being in our modern, light-saturated world.

Conflict of interest
Nothing to disclose

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