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Effects of circadian rhythm disruption on retinal physiopathology: Considerations from a consensus of experts

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Abstract

The circadian rhythms originate within the organism and synchronize with cyclic fluctuations in the external environment. It has been demonstrated that part of the human genome is under control of the circadian clock and that a synchronizer that helps to maintain daily rhythms is Melatonin, a neuro-hormone primarily synthesized by the pineal gland during the night. The chronic disruption of circadian rhythm has been linked to many conditions such as obesity, metabolic syndrome, type 2 diabetes, cancer, and neurodegenerative diseases. Studies in the mice showed that the disruption of the retinal circadian rhythm increases the decline during the aging of photoreceptors, accelerating age-related disruption of cone cell structure, function, and viability and that the melatonin receptor deletion seems to influence the health of retinal cells, speeding up their aging. In conclusion, preserving the circadian rhythms could be to add to the prevention and treatment of age-related degenerative retinal diseases, and although additional studies are needed, melatonin could be a valid support to favor this "chronoprotection action".

Keywords

Circadian rhythm, age related macular degeneration, melatonin, chronoprotection

Introduction

The 2017 Nobel Prize in Medicine or Physiology was assigned to three circadian biologists, Jeffrey C. Hall, Michael Rosbash, and Michael W. Young for their discoveries of molecular mechanisms controlling the circadian rhythm. They recognize the importance of the circadian biological system and its tremendous impact on the life of an organism.

The study of circadian rhythms within the eye is an important topic of investigation. The data thus far collected indicates that circadian dysfunctions produce significant alterations in function and health, implying that a "chronoprotection system" could be a good approach in the prevention of retinal diseases related to aging. Recent literature suggests a possible connection between circadian rhythm and age-related macular degeneration (AMD), one of the leading causes of blindness among the elderly population of industrialized countries.[1]

To investigate this, a group composed of medical retina and pharmacology experts were invited by the European School of Advanced Ophthalmology Studies (ESASO, Lugano, Switzerland) to discuss the importance of biological

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rhythms in ocular health and the possible connection between circadian rhythm and retinal degeneration during aging, especially in the pathogenesis of AMD. After discussing scientific papers, the experts debated the importance of the circadian biological system and its tremendous impact on the life of an organism and, probably, on the retinal diseases related to aging.

This editorial reports what was studied and discussed by the expert group, focusing on some aspects that could potentially impact the prevention and treatment of degenerative retinal diseases.

Circadian system in mammalian

Disruption of the circadian rhythm can alter the physiological activity of an organism and lead to the onset, development, and progression of disease

Daily rhythms are a common feature of living systems. Generally, these rhythms originate within the organism and synchronize with cyclic fluctuations of the external environment. Mammalians possess a body-wide network of endogenous circadian clocks with a period between 20 and 28 h.[1]

Oscillation of the biological clocks is generated through a biochemical interaction of specific proteins, which act on transcription and translation mechanisms to produce periodic changes: i.e. near-24 h feedback-loops in gene expression and protein abundance.[2]

More genes contribute to these feedback-loops and are called "clock genes", but the core functional elements are six genes: Period genes (Per1 and Per2), the Cryptochrome genes (Cry1 and Cry2), and transcription factors Clock and Bmal1.[3] Among these, the key circadian transcription factor is Bmal1. It is the only gene whose removal results in an immediate and complete loss of circadian rhythmicity.

It has been demonstrated that 15–20% of the human genome is under the control of the circadian clock, with tissue-specific variations.[4]

A central pacemaker of the circadian rhythm lies in the suprachiasmatic nucleus (SCN) of the hypothalamus, and the synchronization with the external environment occurs by the light/dark cycle acting via the retina and the retino-hypothalamic projection to the SCN. Then the central pacemaker in the hypothalamic SCN adapts the cellular clocks present throughout the body to the external light-dark cycle.

Studies conducted over the last 10 years have demonstrated that the retinal mechanism that originates the signal is independent of the visual system. It is based on intrinsically photosensitive retinal cells located in the ganglion cell layer (GCL) that contain melanopsin. This light-sensitive protein has a peak absorption at 480 nanometers (in the blue-light wavelength).[5] The chronic disruption of circadian rhythm has been linked to a large number of conditions such as obesity, metabolic syndrome, type 2 diabetes, cancer, and neurodegenerative diseases.[6]

Studies have demonstrated that circadian disruption directly affects biohumoral mechanisms by altering the expression of specific genes. For example, reduced glucose tolerance has been highlighted in night shift workers, suggesting a possible mechanism for the development of diabetes.[7] The World Health Organization (WHO) classifies disruption of circadian rhythms as a probable carcinogen, with epidemiological studies showing a higher incidence of breast cancer in women working night shifts,[8] possibly because of the role that clock-proteins assume in regulating the cell cycle.[9]

Retinal circadian system

Disruption of the retinal circadian rhythm increases the photoreceptors decline during aging, accelerating age-related disruption of cone cell structure, function, and viability

The retina has to adapt to varying amounts of light in the arc of the day. It has an endogenous circadian clock, or more likely a network of hierarchically organized circadian clocks that are present in almost all its cells, including the Retinal Pigment Epithelium (RPE). Moreover, it was demonstrated that the retina also has a complicated autonomous system with which it synchronizes with light and dark through different photopigments.[10] Several studies have demonstrated that the physiological, cellular, and molecular rhythms present within the retina are under the control of the retinal circadian clock.[11]

The changes in retinal function and how this might be affected by circadian cycle disruption were studied using both young and older mice with retina-specific Bmal1 removal.[12] Examination of electroretinograms (ERGs) in Bmal1- mice compared with littermate Bmal1+ controls showed that both scotopic (rod-based) and photopic (cone-based) ERGs in Bmal1- mice exhibit significantly lower b-wave amplitudes in comparison with Bmal1+ mice at 3 months of age.[13] Thus, both rod and cone retinal pathways are affected by retinal Bmal1 disruption.

Examining 24-month-old wildtype mice showed that the amplitude of both scotopic a- and b-waves and photopic b-wave significantly decreased during aging, indicating an effect of aging on photoresponses both at the photoreceptor level and the bipolar cell level.[14]

The responses of aged Bmal1- animals were examined and compared with those of aged control group animals. The age-related decline in the photopic b wave was greater in Bmal1- mice compared with Bmal1+ mice. These results suggest that aging diminishes the ERG response of both rod- and cone-based retinal pathways

and that disruption of the retinal circadian rhythm increases the decline during aging of cone-based bipolar responses.[13]

This explained the ERG data showing that at both young and old ages, the bipolar cell response to scotopic stimulation is reduced by the removal of retinal Bmal1. On the other hand, it was shown that in the retinas of Bmal1- mice, the dendritic processes of rod bipolar cells are stunted at both 3 and 26 months, resulting in decreased efficiency of synaptic transmission between photoreceptors and bipolar cells, while the dendrites of cone bipolar cells appear normal.[13]

A detailed segmentation analysis of retinal layers showed that Bmal1-mice at 26 months exhibited a significant reduction in the number of cone outer segments and cone nuclei compared with younger mice while a significantly smaller reduction in the number of cones was seen in old Bmal1 +mice. Finally, the remaining cones in the 26-mo-old Bmal1-mice had significantly shorter outer-segment plus inner-segment lengths compared with Bmal1+mice.[13–14]

Considering that correlation does not mean causation, it can be suggested that disruption of the circadian rhythm can be linked to degenerative pathologies of the retina associated with aging, such as AMD, affecting mostly cones.

In this context, we cannot overlook the role of the RPE in maintaining retina health nor that accumulating evidence indicates that cellular metabolism is under the direct control of the circadian clock.[15–19]

The RPE is involved in many physiological functions that are key to maintaining photoreceptor health.[1,20] One of the most important roles played by the RPE is the phagocytosis of the disks that are shed by photoreceptor outer segments that are continuously renewed by the assembly of new membranous disks.

This activity follows a circadian rhythm and experimental evidence indicates that the circadian clock controlling disk shedding is in the eye, possibly in photoreceptors, though it seems that the photoreceptors are not the only controllers of disk shedding.[1,21–24]

The peak digestion of the outer segments of rods occurs shortly after the onset of the day while that of cones occurs in the first part of the night.[25] It was shown that circadian clock disablement resulting in the lack of peak in RPE phagocytosis leads to reduced viability of photoreceptors during aging.[26] Moreover, even a small shift in the timing of phagocytosis peak leads to the accumulation of undigested outer segments material, such as lipofuscin, which is implicated in the pathogenesis of retinal degeneration.[27,28]

Melatonin

The action of melatonin as an antioxidant plays an important role in protecting cells from aging

Melatonin is currently used by millions of people to retard aging, improve sleep, reduce jet-lag symptoms, and treat depression. It is a neuro-hormone primarily synthesized by the pineal gland during the night. The synthesis duration is related to the length of the dark period, while light exposure suppresses endogenous melatonin.[29,30] In mammals, melatonin modulates multiple aspects of physiology having receptors expressed in many different organs and tissues, including retinal cells. Melatonin can be considered an endogenous synchronizer that maintains and synchronizes daily rhythms throughout the body. Moreover, it can also act as a free-radical scavenger and thus as an antioxidant.[30,31]

The action of melatonin as an antioxidant is believed to play an important role in protecting cells from aging and some neurodegenerative diseases.[30,31]

Melatonin and mammalian retina

Melatonin can play an important role in retinal aging, biological rhythms, and antioxidation

Melatonin can modulate a wide variety of retinal functions, although the precise mechanisms are likely to vary in a species-dependent manner.[32,33] It may have a profound impact on the function of the molecular clockwork and, at least in some tissues, is not only a clock output, but can also regulate the expression of canonical clock genes. For example, it was observed in the mice that the rhythmic expression of Period1 (one of the clock genes) in the pituitary gland depends on melatonin receptor signaling.[34,35]

In this context, it is important to mention that circadian clocks are directly involved in the regulation of cellular metabolism[16] and, consequently, alteration of the clock in cells with a high metabolic rate, like photoreceptors, may result in adverse outcomes.

The actions of melatonin are mediated by two types of G protein-coupled receptors: MT1 and MT2. These receptors are present in many different retinal cell types. In recent studies, the MT1/MT2 heteromer receptor was found in retinal tissue of mice.[32,36]

A group of mice with MT1 and MT2 deletions to a wild-type mice control group were compared to evaluate the effect of MT1 and MT2 deletion on the viability of photoreceptors. No significant differences were observed among younger mice (3 months of age). In contrast, in older mice (18 months of age) with MT1 and MT2 deletion, a significant reduction in the number of cones was observed, of about 30% compared to the same-age control group. These results support the notion that melatonin receptor signaling may be an important signal to promote cones viability during aging.[36]

The protective action during aging appears to be mediated by the melatonin signaling via MT1/MT2 heteromers. A possible explanation is that the MT1/MT2 heteromer, bound to melatonin during the night, inactivates proapoptotic proteins, implying that Melatonin signaling

protects retinal cells during aging. In addition, it was shown that MT1 removal also leads to ganglion cell death and a rise in intraocular pressure during the night.[37,38]

These results highlight the important role played by melatonin in retinal health, as well as in the circadian cycle, especially in protecting cells from aging. In this regard, there is a growing body of evidence showing a link between AMD pathogenesis and functions in which melatonin plays an important role.[39–41] For example, the changes of circulatory melatonin level in AMD were assessed in nocturnal urinary excretion of 6-sulphatoxymelatonin (aMT6s, index of peak blood melatonin concentration) in patients with AMD vs group of age- and gender-matched controls.[40] The results showed that the nocturnal urine aMT6s level in AMD was significantly lower than that of age-matched controls, suggesting that AMD was associated with a greater decrease of melatonin than typically seen with the normal aging process. By excluding the possibility that the AMD pathological processes interesting the retina could be the cause of low circulating melatonin levels, these results suggested instead that melatonin deficiency can play a role in AMD pathogenesis or at least be considered among risk factors.[40]

Conclusion

Preserving the retinal circadian rhythms, that has an established action of "chronoprotection" could be an important element in the prevention and treatment of age-related degenerative retinal diseases. Disruption of circadian rhythm has a definite role in the aging of the retinal cells, especially accelerating age-related disruption of the cone cell structure and could be linked to degenerative pathologies such as AMD, affecting mostly cones.

The deficiency of melatonin contributes to the circadian dysfunction with some data suggesting that melatonin shortage plays a role in the pathogenesis of AMD.

Current knowledge suggests that Melatonin has an important role during retinal aging for three principal reasons: (1) in adjusting biological rhythms having a profound impact on the regulation of clock genes and clock-controlled genes (2) in a free-radical scavenger, and thus as an antioxidant (3) in maintaining a regular sleep cycle.

Melatonin could be an important component in the "chronoprotection action" in the eyes, but additional studies, preferably a multicentre randomized long-term clinical study, will be needed to evaluate the effect of an eventual treatment strategy based on melatonin supplements.

But, given that melatonin is an important natural neurohormone whose production decreases with aging, starting the treatment of patients in early AMD with melatonin as a food supplement, to prevent worsening of the disease is plausible. This would permit initial observational data to be collected. An epidemiological study investigating the incidence and prevalence of AMD in night shift workers to confirm the role of the circadian cycle in retinal cells in humans would also be interesting.

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