·Review·

The effect of lens aging and cataract surgery on circadian rhythm

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Abstract

• **Many organisms have evolved an approximately 24-hour circadian rhythm that allows them to achieve internal physiological homeostasis with external environment. Suprachiasmatic nucleus (SCN) is the central pacemaker of circadian rhythm, and its activity is entrained to the external light-dark cycle. The SCN controls circadian rhythm through regulating the synthesis of melatonin by pineal gland *via* a multisynaptic pathway. Light, especially short-wavelength blue light, is the most potent environmental time cue in circadian photoentrainment. Recently, the discovery of a novel type of retinal photoreceptors, intrinsically photosensitive retinal ganglion cells, sheds light on the mechanism of circadian photoentrainment and raises concerns about the effect of ocular diseases on circadian system. With age, light transmittance is significantly decreased due to the aging of crystalline lens, thus possibly resulting in progressive loss of circadian photoreception. In the current review, we summarize the circadian physiology, highlight the important role of light in circadian rhythm regulation, discuss about the correlation between age-related cataract and sleep disorders, and compare the effect of blue light-filtering intraocular lenses (IOLs) and ultraviolet only filtering IOLs on circadian rhythm.**

• **KEYWORDS:** circadian rhythm; blue light; crystalline lens; cataract surgery; suprachiasmatic nucleus; melatonin; ganglion cells

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INTRODUCTION

Many organisms have evolved an approximately 24-hour biological clock. This endogenous circadian rhythm is formed by several peripheral oscillators under the control of suprachiasmatic nucleus (SCN) in the anterior hypothalamus. Although the SCN neurons can run autonomously, they require daily synchronization through external time cues. Light, especially short-wavelength blue light, is the most potent time cue in circadian photoentrainment. In 2002, a new subtype of retinal ganglion cells, intrinsically photosensitive retinal ganglion cells (ipRGCs), were discovered[1]. Further study found that a kind of blue light sensitive photopigment named melanopsin expressed in ipRGCs contributed to the synchronization of circadian rhythms with the solar day [2]. The regulation of circadian rhythm depends on a pathway that originates from ipRGCs, *via* the retinohypothalmic tract (RHT) to SCN[3]. In addition, ipRGCs also project to olivery pretectal nucleus (OPN) controlling pupillary light reflex (PLR)[4-5].

Sleep disorders are common among the elderly [6]. It was proposed that age-related loss in lens transmittance and decrease of pupillary area might be important causes of sleep disorders and circadian rhythms disturbance in the elderly[7]. Age-related cataract is the leading cause of reversible blindness and visual impairment throughout the world. It is characterized by lens opacity, which leads to the gradually loss of vision and light transmission with age. Nowadays, it is commonly believed that surgery is the only effective treatment for age-related cataract. In addition to improving vision, cataract extraction with intraocular lens (IOLs) implantation might affect the circadian rhythm and sleep. There were literatures suggested that oxidative stress in the retinal pigment epithelium (RPE) caused by blue light exposure could be an important factor in the pathogenesis of age-related macular degeneration (AMD)[8-9]. Based on this theory, blue light-filtering IOLs was invented and applied in clinical. However, the concern of its potential disadvantages effect on circadian rhythm has been raised.

In this review, we summarize the relevant circadian physiology, highlight the important role of eye in circadian rhythm regulation, and discuss how lens aging and cataract surgery influence the circadian system.

Suprachiasmatic Nuclei-the Master of Circadian System In most living organisms, the daily variations of physiological processes such as behavior, sleep/wake cycle, subjective alertness, cognitive performance, hormone production, and body temperature have a circadian rhythm of

roughly 24h. Under normal conditions, the endogenous circadian rhythm is generated by neurons located in SCN of the anterior hypothalamus. The SCN neurons have an intrinsic electrical rhythm of nearly 24h even in the absence of environmental time cues [10-11]. This rhythm reflects the auto-regulatory transcription and translation feedback loops of the clock genes[12-14].

Although the SCN rhythm can run autonomously, it is synchronized to the daily light/dark cycle [12-13]. Zeitgebers are time cues that phase shift circadian clocks, and light is the most potent zeitgeber in circadian system; however, other non-photic signals can also entrain the circadian rhythm, such as time of food intake, exercise, and social interactions[15]. SCN receives light information from retinal photoreceptors *via* the RHT, and connects to the pineal gland regulating the synthesis and secretion of melatonin [16-18] (Figure 1). In conclusion, SCN synchronizes the internal biological processes with the external time cues to maintain normal physiological functions.

The majority of SCN neurons are GABAergic [17], and they can be divided into two subtypes according to the different neuropeptides they expressed. One subtype expresses arginine vasopressin (AVP), while the other expresses vasoactive intestinal polypeptide (VIP)[19-20]. AVP and VIP act on V1a/V1b and VPAC2 receptors respectively to transmit circadian signals [21-22]. It is believed that different subtypes play different roles. Specifically, VIPergic neurons are involved in receiving RHT and secondary visual inputs, whereas AVPergic neurons amplify the endogenous SCN rhythms into coherent behavioral outputs[23].

The output of SCN is complex with major efferents going caudally into the subparaventricular zone and dorsomedial nucleus (DMN), dorsal efferents to the thalamus, and rostral efferents to the anterior hypothalamus and preoptic area[24-25]. DMN integrates the direct input from SCN and the indirect input from subparaventricular zone, and then projects to other hypothalamic areas to control circadian responses, for example sleep and wake initiation. The efferents to paraventricular nucleus (PVN) mainly regulate the melatonin synthesis by pineal gland.

Melatonin-the Marker of Circadian System Melatonin is a hormone synthesized and released by pineal gland in a cyclic pattern under the control of SCN [26]. The chemical structure of melatonin is N-acetyl-5-methoxytryptamine [27]. Melatonin is synthesized from L-tryptophan, which is converted into 5-hydroxytryptophan and then into serotonin. Serotonin is first transformed into N-acetylserotonin by the arylalkylamine-N-acetyltransferase (AA-NAT), and then transformed to melatonin by hydroxyindole-O-methyl transferase (HIOMT) [28-29]. The AA-NAT is activated by norepinephrine through binding to β-adrenergic receptors[30]. Melatonin is released into circulation once produced by pineal gland. Plasma melatonin concentration is low during the day and high during the night. The 24-hour plasma melatonin profiles provide accurate measurement of circadian phase, specifically, melatonin levels start to increase about 2 to 3h prior to habitual bedtime, remain elevated during the night, peak between 02:00 to 04:00, and rapidly decease in the following hours [31-32] (Figure 2). Dim light is particularly important in the entrainment of circadian rhythm. Two currently used indicators of circadian phase include the dim light melatonin onset (DLMO) and the peak melatonin concentration at night. DLMO represents the onset of the evening melatonin production measured in dim light and is thought to be the most reliable circadian phase marker[31]. Moreover, the normal nocturnal melatonin synthesis can be suppressed and phase-shifted by light, depending on its intensity, wavelength, timing and duration[33-35].

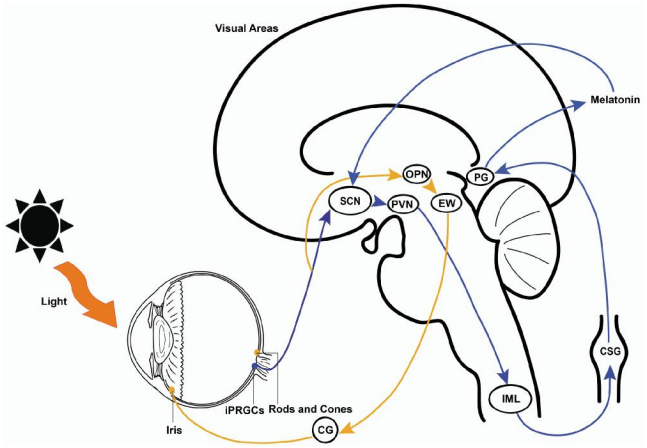

Figure 1 Schematic summary of primary light-induced non-image forming pathways The circadian regulation of melatonin secretion (the blue pathway) and the pupillary response (the orange pathway) depend on pathways originate from the ipRGCs in the retina. ipRGCs receive light stimulus and project to SCN *via* the RHT. SCN sends inhibitory signals to neurons of the PVN. PVN activates the preganglionic neurons of intermediolateral column in the spinal cord, and then projects to the cervical superior ganglion (CSG) activating melatonin secretion by pineal gland (PG). The circulating melatonin binds to melatonin receptors and inhibits SCN neurons from firing. ipRGCs also project to OPN, and form the pathway involving OPN, Edinger-Westpha nucleus (EW), and ciliary ganglion (CG) regulating pupillary responses.

In mammals, actions of melatonin are mediated by two types of melatonin receptors-MT1 and MT2 [36]. Melatonin receptors belong to G protein-coupled receptor superfamily[36]. As melatonin receptors are widely expressed in many organs and tissues, melatonin is involved in modulating multiple physiological activities. The rhythm of melatonin production and the concentration of melatonin in body fluid are reliable markers reflecting the circadian rhythm [37]. And because exogenous administration of melatonin can improve sleep quality, melatonin is thought to be a sleep-promoting agent in the treatment of insomnia[38], delayed sleep phase disorder

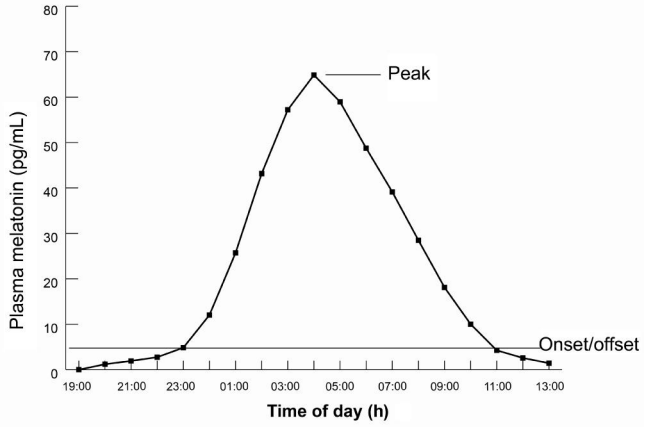

Figure 2 Illustration of plasma melatonin concentrations in a normal subject The DLMO and the peak melatonin concentration are two reliable markers of circadian rhythm. At present, there is no standard calculative method of DLMO. The calculation of DLMO is based on a fixed threshold (time reaching 1-, 3- or 5-pg/mL), a dynamic threshold (2 standard deviations above the mean of 3 baseline samples), or a mathematical model (for example the "hockey-stick" method). The peak is often reached at 02:00 to 04:00.

(DSPD)[39], jet lag and shift work disorders [40]. Moreover, melatonin also acts as a free-radical scavenger [41-42]. This property of melatonin is important in protecting cells from aging and might keep animals and human away from neurodegenerative diseases [41]. Melatonin also has a crucial role in immunomodulation, cardiovascular function regulation and tumor suppression function[43-44].

There is an age-related alteration in nocturnal serum melatonin concentrations [45]. The melatonin level peaks at 3-6y, and then gradually decreases in adolescence. With aging, the melatonin rhythm progressively dampens, with a tendency towards phase-advance [46-47]. Moreover, some studies reported that melatonin concentration decreased in numerous diseases [48-51]. In conclusion, whether the declination of melatonin levels is only age-related changes, or is related to systemic diseases still remains unclear.

Intrinsically Photosensitive Retinal Ganglion Cells –a Novel Photoreceptor in Light Entrainment The mammalian eye is responsible for two main light-induced functions. The most widely recognized function is to provide visual information. However, the non-visual functions, for example circadian photoentrainmen,are of equal importance. Several experimental studies found that genetic ablation of rod and cone photoreceptors in animals didn't affect their circadian responses to light [52-54]. Moreover, clinical findings showed that optic neuropathies selectively affected classic photoreceptors in the outer-layer of retina could result in vision loss with relatively preserved pupillary light reflex and stable circadian rhythm [55-56]. These results suggested that there might be another photoreceptive pathway in the retina regulating circadian rhythm aside from the cones and rods.

In 2002, Berson *et al* [1] reported a novel type of photosensitive ganglion cells in the mammalian retina. These retinal ganglion cells express melanopsin and could depolarize to light stimulation in absence of rods and cones, therefore, they are named ipRGCs. Further study showed that melanopsin gene (Opn4) shared more homogenous sequence with invertebrate rhabdomeric opsins than with vertebrate opsins [57], suggesting that there might be a different mechanism for melanopsin photoreception from rods and cones photopigments in vertebrates [58]. Although ipRGCs comprise only 0.2% -4% of total retinal ganglion cells in mammalian retina [1,59-60], they mediate a broad range of physiological responses and are divided into five types (M1-M5) according to their morphological and physiological properties [61-62]. The M1 cells are the largest and most numerous subtypes. They project predominantly to SCN[63-64], and also project to OPN [65-66]. However, the non-M1 cells show widespread projections to brain areas that involved in image formation. The light response of ipRGCs is different from that of rods and cones. The activation threshold of ipRGCs is higher than rods and cones, and the response latency as well as the duration of firing are longer than rods and cones[59].

Although ipRGCs are directly photosensitive, they also receive input from rods and cones. The detail connections between ipRGCs and other cells in the retina are not completely understood. Current studies discovered that ipRGCs connected to cones *via* the cone bipolar cells, and connected to rods *via* the amacrine cells and rod bipolar cells [67] (Figure 3). The spectral sensitivity of melanopsin is similar in different species with λ_{max} at approximately 480 nm [1,59,68-69]. Light elicits isomerization of 11-cis retinaldehyde resulting in conformational changes in the opsin receptor, which triggers the downstream signal transduction cascade[70].

ipRGCs have roles in both non-image-forming photoreception and image-forming visual function [59]. Specifically, ipRGCs have two primary non-image forming functions: the circadian photoentrainment function *via* retinohypothalamic tract (RHT) projecting to the SCN[1,71], and the regulation of pupil light reflex by projecting to the OPN [63] (Figure 1). ipRGCs also project to intergeniculate leaflet (IGL), subparaventricular zone (SPZ) and ventrall preoptic nucleus (VLP), which provide additional pathways for circadian photoentrainment [4]. For about image-forming visual functions, evidences from recent studies indicated that ipRGCs projected to distinct brain regions involved in spatial and discriminative visual functions [60,72]. The intrinsic mechanism of the melanopsin's contribution to spatial information and visual perception, and whether it works in humans need to be explored, for these may lead to new prospects for restoring vision in patients who loss vision from rod and cone disease.

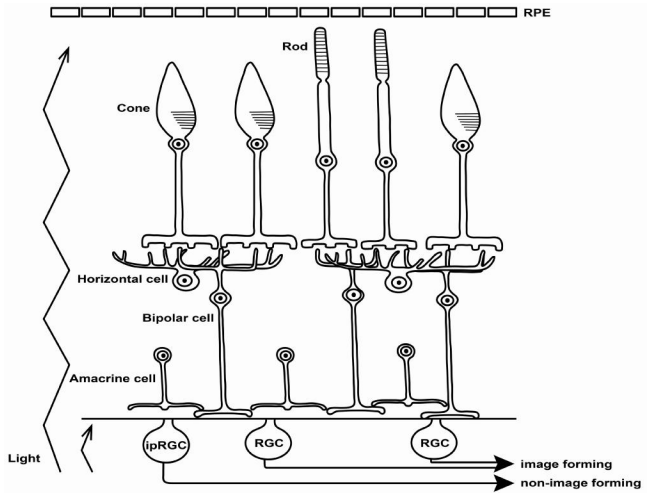

Figure 3 The schematic of ipRGCs and their connections in mammalian retina The ipRGCs can either respond to light autonomously or receive light information from rod and cone photoreceptors in regulating the non-image forming functions. Rods provide inputs to ipRGCs mainly *via* rod bipolar cells and amacrine cells. Cones provide inputs to ipRGCs through cone bipolar cells and amacrine cells (the specific connections are depending on different type of cones and ipRGCs).

Light-the Central Modulator of the Circadian Rhythm It is generally agreed that light is crucial in generating images. Meanwhile, many important physiological activities in human are also influenced by retinal illumination [73-75]. These activities are regulated through independent pathways from image formation. These pathways are referred to as non-image-forming pathways. The most important light-induced non-image forming functions are synchronization of the circadian clock to solar day, tracking of seasonal changes, and regulation of sleep through the rhythmic secretion of melatonin [74]. Light is the most potent time cue (Zeitgeber) in circadian photoentrainment. Beyond these functions, pupil light reflex, body temperature, hormone production, alertness and cognitive functions are also regulated by light.

Light causes phase shifting of the circadian rhythm depending on its duration, intensity, timing and spectrum by regulating the expression of clock genes [76-78]. First of all, studies showed that light administered in late night and early morning could cause phase advancing of the circadian clock. However, light administered in early night could induce phase delay shifts [79-81]. Secondly, regarding to the influence of intensity on the resetting response to light, Zeitzer *et al* [82] found that exposing to intensity greater than room light level in early biological day demonstrated significantly more advancement in circadian clock than exposure to dim light. In addition, Zeitzer *et al* [83] also found that the resetting response and melatonin suppression by light at late biological day related to a non-linear way to illuminance, with minimal responses below 100 lux and saturating responses above 1000 lux. Thirdly, by comparing the phase shifting responses to monochromatic light of different wavelengths with equal photon density, Lockley *et al* [84] demonstrated that both phase shifting and melatonin suppression responses were significantly greater in subjects exposed to 460 nm than longer wavelength. In conclusion, light administered at biological night with high intensity and wavelength lies in blue spectrum is more potent for circadian photoentrainment. Sufficient light exposure at appropriate time is the optimal time cue for circadian photoentrainment, whereas inadequate light exposure could possibly lead to "free-running". Free-running means independent SCN rhythm without daily synchronization and it may lead to circadian rhythm misalignment [85-87]. It was found that many totally blind people had abnormal or non-entrained circadian rhythms due to inability to detect light[88-89]. These patients always suffered from insomnia and daytime drowsiness, which might consequently do harm to psychological and physical health. Exogenous melatonin and melatonin agonist could effectively improve sleep quality and reset circadian clock in these patients[86-87].

The basic biological functions of light give rise to the development of many therapeutic applications. Timed light treatments was shown to be effective for promoting circadian entrainment, improving sleep efficiency, and relieving symptoms of seasonal affective disorder (SAD) and depression[39,90-91].

Lens Aging, Cataract Surgery and Their Effects on Circadian Rhythm Numerous studies showed that the prevalence of sleep disorders is higher in the elderly compared to that in young people [92-93]. A multicenter epidemiologic study that enrolled more than 9000 participants aged over 65y reported that over half of the participants complained about symptoms relating to insomnia [94]. In human, aging is characterized by decreased amplitude of circadian rhythm, advanced phase in circadian rhythm, and disrupted nocturnal sleep [95-96]. These changes of circadian rhythm with age contribute to sleep disorders in the elderly.

Sleep disorders poses substantial risks for the development of many health problems, including cardiovascular and mental disorders, and may contribute to increased morbidity and mortality in the elderly. Therefore, more attention should be paid to improve sleep quality in the elderly [95-96]. Moreover, there are many factors that affect sleep, for example certain physical and psychiatric comorbidities, medications, jet lag and shift work, *etc*.

Any disturbance of the circadian pathway will lead to interruption of the normal circadian rhythm. Therefore, as an important organ in circadian photoreception, the physical and pathological changes of the eye may lead to changes in circadian rhythm. Age-related reduction in responses to light

has been found in both animal and human experiments. It was shown that older rats needed higher light intensity to achieve the same activity rhythm amplitude compared to younger rats [97]. For human, a study investigated the age-related changes in light induced melatonin suppression, and the results showed that the elderly demonstrated significantly reduced melatonin suppression after exposing to short wavelength light compared to the young[98]. However, a recent study showed that in spite of decreased retinal illumination in the elderly, melatonin suppression by nocturnal light exposure was not reduced, however, the peak of non-visual sensitivity shifted to longer wavelengths [99]. So far, the mechanism of how ocular aging affect the circadian photoentrainment is still unclear. More researches are needed to clarify this issue.

Cataract is the leading cause of blindness and visual impairment throughout the world, and age-related cataract is the most common type of cataract. With age, the crystalline lens gradually increases in thickness and weight. The lens nucleus undergoes compression and hardening, and the lens proteins are modified and take on a yellow-to-brown coloration. As a result, the transparency and refractive index of the lens are changed. These changes block the transmission of blue light to retina, thereby reducing the blue light absorbed by ipRGCs [100-101]. Thus, cataract may possibly lead to decreased circadian photoentrainment.

Both *in vitro* and *in vivo* experiments indicated that there was a correlation between lens aging and light transmittance. By evaluating human donor lenses over a wide range of age between 18 to 76y, Kessel *et al* [101] found that increasing age was associated with gradually decreasing transmittance of light, especially at shorter blue wavelengths. In recent years, the development of new apparatuses measuring the transmittance of human crystalline lens *in vivo* showed that the transmission of blue light to retina progressively decreased with age [102-103]. In a word, the aging lens acts as a yellow filter that attenuates blue light reaching the retina and lens aging is thought to influence the circadian photoentrainment. Brondsted *et al* [104] found that the potential for melanopsin stimulation and melatonin suppression were reduced by 0.6-0.7 percentage point per year of life. A cross-sectional population based study by Kessel *et al* [100] found that the risk of sleep disturbances was significantly increased when the transmission of blue light was low. In addition, reduced pupil diameter [105], loss of ipRGCs with age[56], coexistent eye diseases[106] and reduced environmental illumination[107] may all contribute to circadian rhythm disorders in the elderly.

Lens extraction with IOLs implantation is the standard and only effective treatment for age-related cataract. In addition to improving visual function, in theory, cataract surgery is supposed to have a beneficial effect on circadian rhythm regulation for it removes the barrier to short wavelength light optimal for circadian photoentrainment. However, conclusions are inconsistent in different studies. The regulation of circadian rhythms can be measured in various ways, and the most commonly used methods are Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Score (ESS) questionnaires, actigraphy and melatonin concentrations in body fluid. The results of a questionnaire-based investigation revealed that there was a self-reported improvement of sleep quality 1mo after cataract surgery [108]. Another study involved in 961 patients and with longer follow-up time also found an improvement of PSQI overall sleep quality and sleep latency 1mo after cataract surgery, and these effects were sustained at 6 and 12mo postoperatively [109]. Schmoll *et al* [110] reported a reduction of daytime sleepiness after phacoemulsification cataract surgery by using ESS. However, a recent randomized double-masked clinical trial by Brondsted *et al* [111] showed that PSQI global scores and the number of poor sleepers were not affected by cataract surgery. In addition, the study results by Ayaki *et al* [112-113] demonstrated that there was a significant improvement in sleep 2mo after cataract surgery with blue light-filtering IOLs implantation, but thereafter the improvement was not statistical significant; while, the improvement of sleep was found only in poor sleepers after cataract surgery with UV only filtering IOLs.

In regard to melatonin levels, contradictions also exist. Brondsted *et al* [111] found that the peak melatonin concentration at night increased significantly 3wk after cataract surgery regardless of IOLs types, while the majority of circadian and sleep-specific actigraphy parameters did not change after surgery. However, a previous study by Tanaka *et al* [114] failed to demonstrate changes in maximum melatonin concentration and time of reaching maximum concentration after cataract surgery. Further studies of larger sample size and standardized melatonin measurement are required to solve this discrepancies. Considering the small number of participants, various study design, different detecting method and bias, we could draw the conclusion that cataract surgery do not have adversely effect on circadian rhythm and sleep. Further randomized control studies of more participants, longer follow-up time and standard outcome measures are needed to verify the hypothesis that increased photoreception potentiates the input signal to SCN, leading to an improvement in circadian entrainment and sleep quality.

Based on results of animal and epidemiological studies that blue light contributed to the pathogenesis of AMD [8,115], blue light-filtering IOLs were invented and put into clinical use. In recent years, the heated debate regarding to the advantages and disadvantages of blue light-filtering IOLs has never stopped. The blue light-filtering IOLs has lower transmittance of blue light to the retina than the UV

light-filtering IOLs [99-101]. Concerns with blue light-filtering IOLs about its negative effects on circadian rhythms have been raised. It has been found that blue light-filtering IOLs had similar transmittance to that of 53-year-old adults [116]. Some studies suggested that the decreased blue light transmission had negative effects on sleep [117-118]. However, most of the recent studies hold the opinion that blue light-filtering IOLs do not cause significant disruption to the circadian rhythm compared to UV only filtering IOLs[104,111,119-120]. Although blue light-filtering IOLs had lower blue light transmission than neutral UV only filtering IOLs, the clinical effect of blue light-filtering IOLs was relatively small. The results above do not prove that there is no difference between the two types of IOLs except large scale clinical trials and systemic analysis are carried out to determine whether it is better to implant a blue light-filtering IOLs or a UV only filtering IOLs.

CONCLUSION AND PERSPECTIVES

Light is crucial in human health. The eye plays an important role in light-induced non-image forming responses by ipRGCs transducing light information into electrical signals and then transmit to non-visual brain centers including the SCN. SCN is the pacemaker of circadian system and controls many physiological processes. Normal SCN function and sufficient illumination are necessary for maintaining body homeostasis, for example, the normal everyday secretion rhythm of hormones, stable emotions, normal cognitive functions and sleep/wake cycle.

Ocular aging leads to gradually loss of retinal illumination caused by decreasing crystalline lens transmittance and pupillary area, which could consequently limit the photoreception for non-image forming functions. Recent studies found that glaucoma might do damage to the ipRGCs, which could possibly be harmful to the circadian system. Moreover, aging is always associated with numerous systemic diseases that may cause degeneration of SCN neurons or dampen the SCN signals output. All these situations consequently increase the risks of sleeping disorders, psychological illness, dementia, and cardiovascular disease.

Surgery is the only effective treatment for age-related cataract. It removes a barrier to light optimal for both vision forming and circadian phtoreception. In theory, age-related cataract patients might benefit from cataract surgery not only in the improvement of visual acuity, but also in the improvement of sleep quality and circadian regulation. However, the exact effects of cataract surgery on the circadian system are still not well understood. And whether there are different circadian photoentrainment effects in blue light-filtering IOLs and UV only filtering IOLs is also unclear. To further investigate these problems, large scale, randomized controlled clinical trials with standard outcome measures are needed.

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