• Review •

Research progress about the effect and prevention of blue light on eyes

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Abstract

• In recent years, people have become increasingly attentive to light pollution influences on their eyes. In the visible spectrum, short-wave blue light with wavelength between 415 nm and 455 nm is closely related to eye light damage. This high energy blue light passes through the cornea and lens to the retina causing diseases such as dry eye, cataract, age-related macular degeneration, even stimulating the brain, inhibiting melatonin secretion, and enhancing adrenocortical hormone production, which will destroy the hormonal balance and directly affect sleep quality. Therefore, the effect of Blu-rays on ocular is becoming an important concern for the future. We describe blue light's effects on eye tissues, summarize the research on eye injury and its physical prevention and medical treatment.

• **KEYWORDS:** blue light; ocular injury; prevention
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INTRODUCTION

The refractive medium of the human eye's different tissue characteristics have different permeation effects on light when the wavelength is <300 nm. A wavelength between 300 and 400 nm can penetrate the cornea and be absorbed by the iris or the pupil. High energy short wave blue light between 415 and 455 nm is the most harmful. Direct penetration of crystals into the retina causes irreversible photochemical retinal damage[1]. As the harmful effects of blue light are gradually realized by the public, eye discomfort related to blue light is becoming a more prevalent concern. Because of blue light's short wavelength, the focus is not located in the center of the retina but rather in the front of the retina, so that the long exposure time to blue light causes a worsening of visual fatigue and nearsightedness. Symptoms such as diplopia and inability to concentrate can affect people's learning and working efficiency[2]. What is the specific damage mechanism of Blu-ray? This article will review the mechanisms causing damage to the cornea, lens, and retina by Blu-ray light in order to have a better understanding of Blu-ray-induced ocular injury.

Effects of Blue Light on Cornea The cornea lies at the front end of the eyeball and is the first structure that light encounters when passing through the eye. Some studies have shown that the survival rate of corneal epithelial cells after Blu-ray irradiation decreases, while blue light has been shown to increase reactive oxygen species (ROS) production in corneal epithelial cells, activates the ROS-nucleotide-binding domain, leucine-rich containing family, pyrin-domain containing-3 (NLRP3)-interleukin (IL)-1β signaling pathway, and trigger inflammation of human corneal epithelial cells (HCECs) induced by hyperosmotic pressure from NLRP3 and up-regulation of IL-1 beta secretion. Thus, mediated oxidative damage and apoptosis lead to further ocular inflammation and xerophthalmia formation[3-4]. Moreover, the oxidative damage caused by blue light was shown to be reduced by effective antioxidant extract associated-free radical elimination, thus improving the clinical symptoms of the eye surface in a dry eye mouse model[5-6] and further confirmed that blue light is associated with the formation of dry eye. Therefore, topical application of antioxidants can be used as a choice of drug option for blue light-induced dry eyes. Niwano *et al*[7] detected blue light's phototoxicity on corneal epithelial cells using an *in vitro* cell culture experiment. The results show that blue light in the near ultraviolet region may affect the mitotic phase of the corneal epithelial cells in a dose- and time-dependent manner. The microvilli on the epithelial layer of the corneal epithelium lose the support and stability of the tear film, leading to the formation dry eyes. However, blue light's effects on the cornea are not limited to corneal epithelial cells. Blue light irradiation also has a significant inhibitory effect on corneal stromal cell activity, which is also dependent on dose and time. Studies have shown that inhibitory effects may be related to the

influence of blue light on corneal stromal cells autophagy. At the same time, Blu-ray irradiation is also used as a treatment for bacterial keratitis. The 440 nm wavelength blue light combined with riboflavin corneal cross-linking for bacterial keratitis demonstrates that blue light can effectively control the corneal ulcer caused by a *Staphylococcus aureus* infection and is expected to be a treatment for refractory corneal ulcers in the future. The safety and long-term efficacy need to be further studied[8-9].

Effects of Blue Light on Lens Cataracts are one of the leading causes of blindness worldwide, which is the result of lens opacity[10]. As early as the 1980s, people realized that the lens provides not only the main optical power (in diopters) but also can effectively filter short light waves in order to reduce retinal light damage occurrence. The lens contains structural proteins, enzymes, and protein metabolites that absorb short wave light. These substances and derivatives are added to the lens's protein to produce yellow pigments in the lens's protein, causing the lens gradually darkens and turns yellow. The absorption blue light by the lens increases significantly, thus blocking potential blue light retinal damage[11]. However, when it exerts its protective effect on the retina, the lens has to undergo a decrease in transparency or color change, which leads to cataract formation. As we all know, Sunlight exposure is considered to be a risk factor for cataracts. Studies have shown that blue light can induce the production of ROS in the mitochondria of lens epithelial cells (hLECs), which may lead to the development of cataracts[12-13]. In a very recent study, oxidative stress was considered an important medium in the pathogenesis of age-related cataracts. The use of added antioxidants is a reasonable strategy for protecting antioxidant defense systems from oxidative stress, and studies have shown that an increase in antioxidant enzyme expressions in hLECs directly scavenge free radicals in order to reduce hydrogen peroxide's effects. Apoptosis and ROS accumulation can keep the lens clear and slow down cataract occurrence and development[14]. In the eye, carotenoid lutein (L) and zeaxanthin (Z) are effective antioxidants and are the only carotenoids found in the lens. They have the characteristics of compounds that absorb short-wave blue light[15]. Research data show that L or Z can protect the lens's proteins, lipids, and DNA from oxidative damage. During oxidative stress, the redox state of these antioxidants can be improved, thus providing protection for the lens[16].

Effects of Blue Light on Retina Retina is the initial site of vision formation, and it is also the lesion site of various blinding eye diseases. It plays an important role in preventing blindness. Blue light can penetrate through lens to the retina and cause retinal photochemical damage. At present, there are relatively many studies on blue light's effects on the retina, but they are still being debated.

Retinal degeneration and morphological changes The effects of blue light- and light-emitting diode (LED)-induced irradiation on retinal function and morphology were studied by Kim *et al*[17]. The results showed that the a and b amplitude of the electroretinogram decreased after blue light irradiation. After activation of microglia cells, they then migrated to the phagocytic fragment of the outer nuclear layer as seen under the electron microscope. In age-related macular degeneration (AMD) patients, there were many activated microglia infiltrating the outer nuclear layer of the retinal rod-shaped cell death region[17-18], and some studies have shown that blue light can accelerate AMD occurrence and development after cataract surgery that occurred many years previously. In addition, an experimental study about blue light-induced oxidative stress injury on rabbit retinas showed that the rabbit retinas after 24h of blue light irradiation had become disordered in the inner and outer segments of the photoreceptor cells when compared with the normal control group. The outer retinal nuclei were scattered in the edematous cells, and the photoreceptor cells were mildly disordered. The more disordered the cell arrangement, the lower the thickness of the outer nuclear layer[19].

Damage of blood retinal barrier function Other wild mouse models of the retinal leucine zipper transcription factor were compared with the wild mice dominated by the rod cells after the blue light exposure. It was found that a large amount of nuclear condensation appeared in the outer nuclear layer of the wild mice's retina, and additional dead cone cells was found in the retinal core layer of the whole conical cell mice. Outer cone cell death, accompanied by a full layer of macrophages and activated microglia, has been shown to mediate the blood retinal barrier function impairment by releasing a variety of pro-inflammatory factors, including tumor necrosis factor (TNF) and IL-1, and they have detected blue light-induced retinal edema in two mouse models through fundus imaging and optical coherence tomography (OCT). As a result of pro-inflammatory factor release, blood vessels' permeability is increased, and some harmful components of the blood such as immune complexes and lymphotoxin are extruded into the retina[20-21]. Zhao *et al*[22] speculated that part of the cell death may not be a direct consequence of blue light exposure but is indirectly caused by the exudative blood components' toxicity, and blood component participation can be proven. The severity of the inflammatory response and control of the severity of photoreceptor cell degeneration suggests that blue light can indirectly cause inflammatory reactions and photoreceptor cell damage after the destruction of the blood retinal barrier.

Oxidative stress injury of the retina Lipofuscin is the residue of the retinal pigment epithelial cells phagocytic and digestible rods and conical cells. With increasing age, the secondary enzyme of the retinal pigment epithelium has

been shown to increase. Recently, the N-yellowy-N-retinoid-ethanolamine (N-retinyl-N-retinylidene ethanolamine, A2E) is lipofuscin's core fluorescent group. In non-degradable pigments, it shows strong absorption of blue light through oxidative stress-mediated retinal pigment epithelial cells apoptosis and necrosis[23-24]. Mitochondria are the main targets of blue light-associated oxygen free radicals. Under aerobic conditions, blue light stimulates the mechanism of retinal initiation and oxidation, induces a large number of free radicals, destroys messenger ribonucleic acid (mRNA) and proteins, causes necrosis of photoreceptor cells and pigment epithelial cells, and destroys the dynamic balance of the body's normal redox state. Under conditions of severe oxidative stress, the retina ganglion cells (RGCs) present a large number of mitochondria in the intraocular axons and photoreceptors. The macular carotenoids in the Henle layer of the inner layer of the photoreceptor absorb short wave blue light, which occurs between 400 and 480 nm, so that blue light-induced damage to the RGCs' mitochondria is substantial. Extensive receptor interacting protein (RIP)1/RIP3 activation was shown to induce RGC death, thus causing speculation that the RIP kinase inhibitor can be used as a neuroprotector to lessen blue light-induced cell necrosis[25-26]. The mechanism of light damage to the retina by blue light was labeled by Ishii and Rohrer[27] as the "bystander effect" because it is triggered by single cell photo-oxidative stress, which induces biological effects in non-targeted cells. Blue light stimulates local oxidative stress in single cells of the retinal pigment epithelium and causes an active ROS-induced signal. The radiation spreads rapidly to the periphery, while the Ca^{2+} signal was slowly and unevenly transmitted to adjacent cells, which induced changes in the mitochondrial membrane potential. Finally, the metabolic characteristics of the high baseline Ca^{2+} levels led to localized cell damage in the retinal pigment epithelial cells[27]. In addition, the experimental results showed that blue light could induce degradation of retinal pigments. The mRNA and protein expressions of the L type calcium channel alpha 1D subunit in the skin cells and both vascular endothelial growth (VEGF) and basic fibroblast growth factor concentrations increased, and the alpha 1D subunit protein expression was positively correlated with the VEGF concentration. Therefore, Li *et al*[28] believed that the alpha 1D subunit may be involved in blue light-induced injury in retinal pigment epithelial cells.

Effects of Blue Light on Refractive Development Epidemiological evidences show that outdoor activities can prevent the occurrence and development of myopia[29], but the lower myopia rate has no obvious correlation with the amount of near work time and the intensity of outdoor activities[30]. A survey of the impact of screen reading on schoolchildren' visual acuity was recently conducted. The results show that screen reading can lead to the occurrence and development of poor eyesight in schoolchildren, and the higher incidence of nearsightedness correlates with the increase in the length of the screen reading time[31]. From the difference between screen reading and outdoor activities, we found that outdoor activities are exposed to natural light, which is more concentrated in short-wave blue light than other artificial light sources. The study of Rucker *et al*[32] suggested that sunlight is much richer in short-wavelength light than most artificial illuminants, which turned to reduce the eye length through the mechanism of retinal dopamine release. In addition, the research also showed that blue light was essential for the reduction in astigmatism during development. Experiments done in animal have shown that monochromatic short-wave blue light inhibited the growth of the eye axis and the glass cavity in guinea pigs to produce a relative hyperopia[33-35]. It was also shown that myopia could be rapidly reversed to hyperopia after blue light irradiation, which could help to explain blue light can affect refractive development and reverse myopia[35]. In addition, the study showed that short wave blue light is involved in the refractive development of the guinea pig by inducing an increase of retinal cone density and retinal expression, but the specific cause and effect is not clear. It will be necessary to do additional studies[36].

Effects of Blue Light on Circadian Rhythm Numerous studies have shown that blue light can regulates the body clock and promote alertness, memory and cognition. The main mechanism is that blue light stimulates the secretion of melatonin in pineal gland which can increase or decrease cortisol expression depending on time of day and regulate human circadian rhythm[37-39]. There were researchers have investigate the sleep quality found that after cataract surgery the sleep quality of old people have improved to some extent, the reason is that transparent artificial crystal allow more blue light penetrate to reach the eye[40] and thus confirmed that blue light can regulate the circadian rhythm. However, if blue light is excessive, especially at night when melatonin production peaks, it can not only damage the retina through the ocular surface, but can also stimulate the brain, inhibit melatonin secretion, and increase corticosteroid production, thereby destroying hormonal secretion and directly affecting sleep quality[38]. As recently as ten years ago, some scholars suggested that a variety of sleep disorders appear to be closely related to visual impairment, suggesting that sleep quality is related to eye diseases[41]. Sleep disorders cause an increase in corticosteroid production[38], which can reduce parasympathetic nerve excitability and reduce tear secretion, thus causing the occurrence of dry eyes. At the same time, blue light-induced sleep disorders cause a reduction in eye closing time, and after a longer period of time, open eyes will cause an increase in tear evaporation thus leading to dry eye symptoms. In addition, some studies have shown that lack of sleep can

reduce the body's androgen levels[42]. There have been a large number of studies that have shown that the lack of androgens can lead to the dysfunction of the eyelid's gland function, thus reducing the lacrimal lipid layer's secretions and leading to the occurrence of excessive evaporation of dry eyes[42-43].

Prevention of Blue Light-induced Injury With the improvement in working and living conditions and the changes in people's life styles, more and more exposure to blue light has occurred. The prevention and control of blue light damage is becoming more and more important, and the anti-blue light products are constantly emerging. Under what circumstances do we need protection from blue light? It is unscientific to equate all blue light as directly causing eye injury and unilaterally, and a certain degree of blue light can not only improve the control of dark room, slow the growth of eye axis, prevent the occurrence and development of myopia, and also regulate circadian rhythms[37-39]. In addition, as a reference to the most extensive standards set up for daily light intake, scientific research has shown that normal digital displays present minimal risks, and most of the displays are within the standard range, but this is only a conclusion with respect to short-term exposure. It is necessary for us to take a series of anti-Blu-ray measurements after long-term exposure. We should minimize the use of electronic devices at night and avoid the effect of blue light on the secretion of melatonin at night, so as to ensure good sleep and eye closure time[37-39]. In addition, when we use blue light rich product at night, the approved anti-blue light glasses or screen cover may be a good choice to avoid blue light-induced injury. According to the mechanism of blue light damage, we are able to use antioxidant base scavengers, enzyme activity protectors, and optic neuroprotective agents[8-9] for protecting our eye tissue, but the specific drugs and effects still need to be further studied.

In summary, a certain extent blue light can promote human eye refractive development and regulate circadian rhythm, but harmful blue light-induced effects on human eyes should not be ignored, blue light can also produce different degree of damage to corneal, crystal lens and retina. Therefore, it is necessary to take appropriate protective measures when using blue light-related products, especially at night.

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