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Can Blue Light Increase The Risk Of Macular Degeneration Or Affect Visual Performance?

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Abstract

Recently the effects of blue light exposure are becoming more prevalent in recent years due to the development in technologies and are becoming a major concern among the general public. Blue light can be emitted from many sources including the sun, phone screens, computer screens, and even LED lights. Wavelengths ranging from 415 nm to 455 nm have been known to cause eye damage. It is known that blue light can affect the cornea and the retina. The damage is not only limited to the eye though, the damage could also be done on the DNA level where blue light can alter the regulation of numerous genes. Although the effects of blue light may sound scary, there are ways to help reduce or prevent blue light-induced injuries, this may include using blue light filter spectacles, or screen protectors. These preventatives can help reduce computer vision syndrome while also helping prevent phototoxic retinal damage.

Keywords: Blue light; lipofuscin; age-related macular degeneration (AMD); visual performance

Introduction

Recently, as lighting technology has improved, people are now more exposed to artificial lighting including mobile phones, LED lights, computers, and other devices (1, 2). Blue light is a part of the visible light section in the electromagnetic spectrum, with a wavelength ranging from 400 nm to 500 nm (3). Ultraviolet and blue light's negative effects ultraviolet light is the fraction of the visible light spectrum between 286 and 400 nanometers that is thought to be detrimental to the eye, perhaps causing cataracts and other eye illnesses like age-related macular degeneration (AMD) (4, 5). Damage to the retina in the eye is the most prominent hazard from light (6). Thermal, structural and photochemical are the three types of retinal damage (7). The wavelength, intensity, and exposure period all influence the type of damage that occurs (7). While most ultraviolet light comes from the sun, other sources such as welder's flash, digital display, fluorescent lighting, high-intensity mercury vapour lamps, and xenon arc lamps can be a source of ultraviolet light as well (8). This literature review aims to explore and discuss the effects of blue light on the human body especially the cornea, and the retina in the eyes and raise awareness in order to encourage people to take care of their visual health.

Types of blue light and its effects on the eye

UV light is divided into three different categories: A, B, and C. To begin with, the earth's ozone layer effectively filters UVC (below 286 nm) (9). Second, UVB (286-320 nm) is a type of solar energy that is absorbed by the cornea and causes sunburn and snow blindness (9). Finally, UVA (320-400 nm) is the component of the invisible spectrum that eye care practitioners are most concerned about (9). It is the most harmful type of UV radiation because it is passed via the human eye's crystalline lens (10). Blue light has been linked to the beginning or advancement of macular degeneration and other eye diseases like cataracts, according to scientific data (7,

11). The blue light emitted by the sun, however, differs greatly from the blue light emitted by electrical equipment (12). While the majority of research indicates that wearing UV-blocking sunglasses is a vital precaution against exposure to sunlight, the study about blue light emitted from digital devices say otherwise and is inconclusive (13). As the public becomes more aware of the impacts of blue light, discomfort and irritation of the eye related to blue light are rising concerns (10). Because of the short wavelength of blue light, the focus is at the front, this causes visual fatigue and nearsightedness to worsen. People's ability to learn and work can be affected by symptoms such as diplopia and inability to concentrate. Retinal lesions which are caused by Blue light (441 nm) was first reported in 1978 and this happens by photochemical damage and not from thermal injury (10). Overexposure to blue light appears to cause a significant increase in ROS generation, which contributes to photoreceptor loss, lipid peroxidation, and cell death (14, 15). The dangers of blue light have recently gotten a lot of press, and the strive for new preventive and restorative measures to reduce blue light hazards has become important research regarding the discipline of ophthalmology (16). To date, many attempts have been undertaken to try to minimize the phototoxicity of blue light (17). Currently, there are various anti-blue light products available including anti-blue light glasses (1, 18). Furthermore, new techniques such as gene therapy, retinal transplantation, and antioxidant base scavengers, have also been proposed by some scholars (18-20).

Effects of blue light on the cornea

The cornea is the first structure light encounters as it passes through the eyeball and is located at the front end of the eyeball (21). Some studies have found that following Blu-ray irradiation, the rate of survival of the corneal epithelial cells falls, whereas, in the epithelial cell of the cornea, blue light can activate the production of free radicals such as reactive oxygen species (ROS) (13, 22). ROS is involved in the inflammatory signalling pathway through interleukin 1 beta and through the NLRP3 pathway (23, 24). Through these two pathways, an increase of apoptosis of cells in the eye is possible by overexpression of interleukin 1 beta (25, 26). Furthermore, the oxidative damage caused by blue light was shown to be reduced by an effective antioxidant extract related to free radical elimination, as a result, improved symptoms of the eye surface in a dry eye mouse model, verifying that there is a correlation between blue light and the development of the dry eye (22, 27). As a result, an antioxidant topical treatment can be employed as a medication alternative for blue light-induced dry eyes (28). There was a study that used *in vitro* cell culture experiment to detect blue light's phototoxicity on the epithelial cell of the cornea (14, 29). According to the findings, blue light near the UV region has a dose- and time-dependent effect on the mitotic phase of epithelial cells of the cornea (25, 30). When the microvilli on the corneal epithelial layer lose their ability to sustain and stabilize the tear film, this results in dry eyes (29). The effects of blue light on the cornea are not confined to epithelial cells in the cornea (29). Blue light exposure has a considerable hindering effect on corneal stromal cell activity, which is dosage and duration-dependent according to a study (31, 32). Blu-ray irradiation is also utilized as a treatment for bacterial keratitis at the same time. Blue light with a wavelength of 440 nanometers mixed with riboflavin corneal cross-linking for bacterial keratitis reveals that blue light may successfully manage the corneal ulcer caused by a *Staphylococcus aureus* infection and could one day be utilized to treat resistant corneal ulcers (33). Further investigation into the safety and long-term efficacy is required (33, 34).

The effect of blue light on the retina

The retina, as a light receptor, is critical for visual development. The retina contains two distinct cells that contribute to vision formation: retinal pigment epithelial cells (RPE cells) and photoreceptors (the cone and rod) (35, 36). Photoreceptors' primary job is detecting photons of light and converting them to a detectable signal (6, 37). Between the upper layer of retinal nerve cells and the choroid are the RPE cells (22). They are involved in many aspects of eye development and optical function, including growth factor secretion, antioxidant protection, phagocytosis of photoreceptor outer segment fragments, and maintenance of the blood-retinal barrier (36, 38). Thus, maintaining the correct function of photoreceptors and RPE cells is critical for developing vision (36). The effects of exposure to blue light and LEDs on the function of the retina and morphology have been hypothesized (6, 39). The

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results indicated that blue light irradiation lowered the electroretinogram amplitudes (40). When activated, the movement of microglia cells to the phagocytic portion of the outer nuclear layer can be seen using an electron microscope (41). There were numerous activated microglia infiltrating the outer nuclear layer of the retinal rod-shaped cell death region in patients with age-related macular degeneration (AMD), and some studies have shown that blue light can accelerate AMD occurrence and progression following cataract surgery performed years ago (42, 43). Furthermore, when rabbit retinas were exposed to blue light for 24 hours, the inner and outer sections of photoreceptor cells became disorganized, compared to the normal control group, according to an experimental study on oxidative stress injury caused by blue light (44, 45). In the edematous cells, the outer retinal nuclei were dispersed, and the photoreceptor cells were disordered (46). The more disorganized the cell organization, the thinner the outer nuclear layer (47).

Lipofuscin and blue light hazard

What is required for the retina to operate normally physiologically is for the RPE cells to perform phagocytosis of severed photoreceptor outer segments (48). Lipofuscin is detected in undigested membranous discs and lysosomal storage bodies (49, 50). Lipofuscin's primary component is A2E and its oxidation products (51, 52). A2E exhibits spontaneous fluorescence properties as a potential photosensitizer (52). A study conducted tests on RPE cells using blue light of 480 nm and observed that blue light-induced cell death occurred only in cells carrying A2E; those without A2E remained alive (53). Photochemical processes in A2E produce molecules that can produce ROS, which can cause oxidative stress (22). Additionally, the blue light danger was concentration-dependent manner (54).

The blue light hazard pathways in the retina involving lipofuscin are as follows:

Inflammatory reaction

Exposure to blue light can significantly enhance ROS production (14). Inflammatory factors, such as interleukin 1 (IL-1), tumour necrosis factor-α (TNF-α), caspase-1 and MCP-1, can be released when ROS levels are elevated, resulting in the breakdown of the blood-retinal barrier and the onset of inflammation (1). Additionally, blue light-mediated apoptosis in RPE cells requires activation of the NLRP3 inflammasome (55, 56). The RPE cells primarily activate the microglia, and NLRP3 mediates caspase-1 and IL-1 buildup in the microglial cells, resulting in macrophage recruitment to the RPE choroid blood vessel damage and photoreceptor loss (24, 26, 57).

DNA damage

Blue light has been shown to have a direct effect on DNA (58). Blue light induced double-stranded DNA breaks and a significant buildup of DNA breaks in RPE cells (42, 59). Additionally, singlet oxygen may cause mtDNA damage in addition to nDNA damage (42). Additionally, because mtDNA is not protected by histones and its damage repair system is inefficient compared to that of nDNA, it is more susceptible to light risks (60). Additionally, the damaged mtDNA impairs the mitochondrial respiratory chain's integrity, resulting in a cycle of ROS-mediated mtDNA damage (38).

Mitochondrial damage

Mitochondria have long been regarded as the cell's critical energy organ and the primary switch that initiates cell death, also known as apoptosis (61, 62). According to emerging research, microsomes appear to be a target of blue light harm (63). After blue light exposure, TEM images revealed that mitochondria have inflated states with damaged membranes, and the inner cristae vanish (63). The mitochondrion is the target organelle of ROS (22). Blue light with a shorter wavelength raises the number of ROS within cells and promotes oxidative stress(25). Changes in the expression of mitochondrial dynamics-related proteins, as well as an increase in the expression of the mitochondrial mitotic protein Drp1 and a decrease in the expression of the fusion protein Mfn2, cause mitochondrial fission in response to excessive ROS (25, 56). Additionally, blue light can disturb mitochondrial calcium homeostasis by reducing the transmembrane potential (MMP) and increasing the permeability of the mitochondrial membrane (56). Cytochrome C and apoptosis-inducing factor 1 (Apaf-1) are released from mitochondria into the cytoplasm, activating caspase-7, caspase-6, and caspase-3 downstream precursors (63). Programmed cell death necessitates the activation of the caspase protein (64). Furthermore, retinal ganglion cells have a lot of mitochondria (64). High-energy blue LED

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light has been shown to impair mitochondrial function by reducing ATP levels and activating AIF and heme oxygenase-1 (ho-1), which could lead to glaucoma and diabetes (65, 66).

Lysosomes damage

Lipofuscin increases in lysosomes with age via phagocytosis (67). By inducing oxidative stress, blue light-activated A2E impairs lysosomal autophagy function (68). This process has been linked to increased expression in lysosomal-related genes and permeabilization of the lysosomal membrane, as well as cytosolic leaking of lysosomal enzymes (69). In short, when the retina is stimulated with blue light, lipofuscin, the primary chromophobe, creates monomeric oxygen, hydrogen peroxide, and hydroxyl free radicals (1). As a result, it generates inflammation and DNA damage, impairs mitochondrial and lysosomal function, and triggers death in cells via the caspase cascade (42).

Rhodopsin and blue light hazard

Rhodopsin combines 11-cis-retinal and opsin to act as a chromophore in rod cells (70). In the retina, rhodopsin is essential for light reception and the generation of dark vision (1, 71). The chromophore for light damage is now known as rhodopsin (70). Mice without rhodopsin were protected from blue light damage, but mice lacking rhodopsin experienced significant light sensitivity after being exposed to blue light (6). Through a photoreversal bleaching process, blue light can repair activatable rhodopsin and improve its photon absorption capacity (6). Furthermore, changes in the location of rhodopsin from the inner and outer segments to the ONL activated the transcriptional activator AP-1 in photoreceptor cells, causing death (63, 72). In conclusion, rhodopsin causes blue light-induced harm via reversing bleaching (63).

Growth factors and blue light hazard

Blue light exposure has been linked to increased secretion of neovascular factors in the retina, including pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor (VEGF) (73). The balance of PEDF and VEGF in the normal state regulates the neovascularization and permeability of the vessels (74). Additionally, PEDF can inhibit the function of VEGF, thereby inhibiting vascular endothelial cell proliferation (57). Melanie Marie discovered that activating L-type calcium channels allowed the photosensitizer A2E to increase VEGF mRNA levels and decrease PEDF levels in A2E-loaded RPE cells (53). As a result, VEGF and PEDF's dynamic equilibrium is disturbed (71). VEGF activity augments the toxicity of blue light on RPE cells significantly (22, 53). These results suggest that blue light exposure induces vascular dysplasia and increases vascular permeability (22). Hepatocyte growth factor (HGF) is a multifunctional growth factor that promotes the proliferation and migration of numerous ocular cells (75). As a result, it protects the retinal pigment epithelial (RPE) cells and neurons (76). Blue light exposure reduces the level of HGF mRNA in the RPE and retinal neurons, elevating the toxicity of blue light (1). Consequently, blue light irradiation may distort VEGF and PEDF and inhibit HGF secretion, effecting in the progression of eye diseases such as diabetic retinopathy (DDR) and glaucoma (67).

Related genes of blue light hazard

Numerous studies have shown that blue light exposure alters the regulation of numerous genes (77). The caspase-dependent apoptotic pathway primarily harms blue light (78). By exposing them to LED light, caspase-3 and caspase-9 are activated (79). These events could be related with lysosomal membrane permeabilization (69). Bcl-2 and Bax are critical regulators of the apoptotic process in mitochondria (79). Bcl-2 is an anti-apoptotic protein found in mitochondria's outer membrane, inhibiting cytochrome C release. In the cytoplasm, Bax is an apoptotic protein (79). It is transported to the mitochondria in response to an apoptotic signal (78). It enhances the synthesis of cytochrome C (74). Exposure to blue light for an extended period increases Bax expression and decreases Bcl-2 expression, both of which are associated with GADD45 overexpression (64). GADD45 upregulation may occur via the PI3K/AKT and p53 pathways, whereas apoptosis is promoted via activation of the MKK/JNK and mitochondrial apoptosis pathways (80). The JNK and p38 pathways have also been shown to be activated when blue light is used (81). When this happens, c-jun and c-fos can be phosphorylated, which causes cells to die (81). Surprisingly, NF-E2-related factor 2 (Nrf2) has been shown to protect retinal tissues from endogenous and external stresses as a transcription

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factor involved in the stress response (82). Following blue light irradiation, excessive ROS activates Nrf2, protecting retinal pigment epithelial cells from oxidant-induced cell death via the mitogen-activated protein kinase (MAPK) pathway (83). Because of its role in protecting the retina from oxidative stress, ROS activates Nrf2 and the MAPK pathway to keep intracellular REDOX in balance (84). Additionally, blue LED light-induced endoplasmic reticulum stress contributes to retinal damage (85). Excessive light exposure aggregates S-opsin and increases CHOP and GRP78 expression, activating the ER stress (ERS) and unfolded protein response (UPR) signalling pathways (41). Excess light activates PERK, which further decreases ElF2 expression while increasing ATF4 (68). ATF4 can activate two critical target genes—CHOP and CADD34—thereby regulating the expression of apoptotic-related genes (1).

Other mechanisms

There is an unsaturated fatty acid called docosahexaenoic acid (DHA) in RPE cells (60, 86). Singlet oxygen and hydrogen peroxide may be involved in the lipid peroxidation of DHA, resulting in the formation of HOHA (86). By damaging mitochondria and lysosomes, HOHA generally induces apoptosis in cells (51). Furthermore, HOHA serves as a prelude to CEP (51). The immunological response to CEP results in the generation of interferon (IFN-γ) and interleukin-17 (Il-17) by CEP-specific T cells, which causes cell inflammation (52). Between the retinal cells and choroid, RPE cell tight connections form a blood-retinal barrier (74). The blood-retinal barrier is critical for nutrition, water, and electrolyte transport (74). Blue light impairs barrier function by inhibiting the production of the scaffold protein Zonulae occludentes-1 (zo-1) via the PKC-ζ pathway (45). It lowers the survivability of trigeminal neural cells, affects primary neural cell culture, and accelerates cell death (76). Additionally, oxidative stress caused by LED illumination increased the expression of unfolded protein response genes (41).

Prevention of Blue Light-induced Injury

The importance of preventing and controlling blue light harm continues to grow, and anti-blue light products are being developed and released to the public continuously (18). It is erroneous to believe that all frequency of blue light immediately and unilaterally causes injury to the eye (87). A precise number of blue light can improve dark room control, delay eye axis growth, delay the onset development of conditions such as myopia, and regulate circadian rhythms (88). Additionally, based on the most comprehensive standards for daily light utilization, scientific research indicates that standard digital monitors or displays pose negligible hazards when used within the standard range, but this is only a conclusion based on short-term exposure (56). Following prolonged exposure, researchers must take anti-Blu-ray measures (89). Researchers should limit our use of digital devices at night and avoid the potential adverse effect of blue light on melatonin secretion to ensure adequate sleep (66). Additionally, using devices with a high level of blue light in the dark or at night, it is prudent to wear approved anti-blue light glasses or screen protectors to help protect us from blue light-induced injuries (90). Antioxidants, enzyme activity protectors and optic potential therapeutic drugs can all be used to protect our eyes from blue light damage, but specific treatments and consequences need to be studied further (63).

Blue light-filtering spectacle lenses with various degrees of protection from short-wavelength light (ranging from 10% to 100%) are gradually being promoted to the general public to reduce eye fatigue and strain while attempting to prevent phototoxic retinal damage (46). Over the last ten years, the widespread market adoption of ambient light such as compact fluorescent lamps (CFLs) and white-light LEDs in smartphone and tablet computer displays has raised some concerns about their safety and tolerability (91). As a result of the preliminary research, blue-filtering spectacles are being developed to reduce short-wavelength retinal toxicity by insulating the lenses with a dye that absorbs blue and violet light (ranging from 400 to 500 nm) (91). In contrast, regular sunglasses block UV rays with a wavelength of up to 380 nm (92). It has been revealed that the involvement of a yellow chromophore diminishes blue light transmission; additionally, it has been indicated that the proposed of the previously stated protective layer to the anterior and posterior lens surfaces selectively filters the blue-violet light spectrum (415 to 455 nm) (92). Apart from their protective effect on the retina, it has

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been hypothesized that blue filtering spectacles may help alleviate symptoms of eye fatigue associated with prolonged computer use (52, 93).

Conclusion

Blue light is commonly the most damaging to the retina and ocular surface. A blue light injury is caused by various mechanisms, including oxidative stress, mitochondrial apoptosis, inflammatory apoptosis, apoptosis of mitochondria, and DNA damage. Blue light's damaging effects on the human eye should not be overlooked; blue light can also cause varying degrees of damage to the cornea, lens, and retina. As a result, it's critical to take adequate precautions when utilizing blue light-emitting devices, particularly at night.

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