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The impact of light properties on ocular growth and myopia development

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Abstract:

The objective of this article is to comprehensively review the effect of environmental lighting on ocular growth and refractive status in both animal and clinical studies, with an emphasis on the underlying mechanisms. This review was performed by searching research articles and reviews utilizing the terms "myopia," "light therapy," "axial length," "refractive error," and "emmetropization" in PubMed datasets. The review was finalized in December 2023. In the animal studies, high lighting brightness, illumination periods aligning with circadian rhythm, and color contrast signals including multiple wavelengths all help regulate ocular growth against myopia. Long wavelengths have been found to induce myopia in chicks, mice, fish, and guinea pigs, whereas shorter wavelengths lead to hyperopia. In contrast, red light has been observed to have a protective effect against myopia in tree shrews and rhesus monkeys. Apart from wavelength, flicker status also showed inconsistent effects on ocular growth, which could be attributed to differences in ocular refractive status, evolutionary disparities in retinal cone cells across species, and the selection of myopia induction models in experiments. In the clinical studies, current evidence suggests a control effect with red light therapy. Although the lighting conditions diverge from those in animal experiments, further reports are needed to assess the long-term effects. In conclusion, this review encompasses research related to the impact of light exposure on myopia and further explores the retinoscleral signaling pathway in refractive development. The aim is to establish a theoretical foundation for optimizing environmental factors in lighting design to address the epidemic of childhood myopia.

Keywords:

Axial length, emmetropization, light therapy, myopia, refractive error

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Introduction

Myopia is a prevalent condition, particularly with a high prevalence rate in Asian regions. In Taiwan, the prevalence of myopia has experienced a rapid increase among schoolchildren from 1983 to 2017,[1] and in adults, it has surged from around 20% to over 80% in the past 60 years.[2] Based on estimates from the literature, nearly 50% of the global population is projected to have myopia by 2050, with 1 billion individuals at risk of vision loss due to high myopia-related complications.[2] The elongation of the eyeball in high myopia is associated with various ocular pathologies, including retinal detachment, macular degeneration, glaucoma, and early-onset cataracts, most of which lead to irreversible vision loss. This poses a significant economic burden and underscores myopia as a global public health concern. Hence, there is a pressing need to explore effective methods for myopia control.

The current methods available for controlling myopia progression include pharmaceutical interventions and optical approaches.[3-5] Pharmaceutical control typically involves the use of long-acting atropine eye drops, which have shown good efficacy in myopia control. However, they come with side effects such as photophobia and near blur, with increased side effects associated with higher drug concentrations. Patient

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compliance and rebound effects after discontinuation should also be considered. Optical control methods include overnight orthokeratology, contact lenses, or spectacle lenses. These optical designs, such as peripheral defocus, concentric dual focus, progressive multifocals, highly aspherical lenslets, and defocus-incorporated multisegment lenses, aim to reduce the risk of inducing axial elongation by altering high-order aberrations. Orthokeratology and contact lenses are relatively invasive treatments with potential corneal complications and infection risks. The effectiveness of spectacle lenses, mainly studied by the sponsoring companies, requires higher expenditure, and long-term control effects need further investigation.

Previous animal experiments have demonstrated that lighting conditions can impact ocular development and refractive status. The recent surge in research on employing red light for myopia control in children is notable.[6] However, findings from animal and human experiments are not consistent. Therefore, we conducted a comprehensive literature search for publications focusing on the illumination light properties and their myopia control effects. The synthesized results were presented narratively, summarizing key findings and trends across the selected studies. To better elucidate research considerations of myopia, this review incorporates animal experimental models of myopia, methodologies employed in animal and clinical studies, the influence of light properties on myopia, and the signaling molecules in the visual pathway and ocular growth regulation. The results of this study may provide insights into the ideal lighting design as a new option for myopia treatment.

Review

Animal experimental models of myopia

Many species have been utilized as experimental models for myopia, including primates such as macaques and marmosets, vertebrates such as tree shrews, guinea pigs, mice, chickens, and fish, and invertebrates such as squids.[7-13] Despite variations in ocular anatomy, visual acuity, and color sensitivity among these species, the process of ocular development remains relatively consistent throughout vertebrate evolution.[14] From an experimental perspective, each species offers distinct advantages for studying the mechanisms governing eyeball growth and regulating changes in refractive error. However, when interpreting results and applying them to humans, differences in ocular structure and physiology must be taken into account.

In vertebrates, the presence of retinal cells and neural signaling pathways is a common feature, whereas primates such as marmosets, rhesus macaques, and humans possess a fovea centralis, which allows for acute vision. In contrast, other species have an area centralis or a visual streak, which are regions of the retina with high concentrations of photoreceptor cells and ganglion cells. In addition, there are differences in retinal vascular anatomy and the types of photoreceptor cells, as well as their peak sensitivities to various wavelengths of light.

The various species listed above have been demonstrated to develop myopia under conditions of visual form deprivation[15-17] or as a compensatory response to optically induced myopic or hyperopic defocus.[8,18,19] Moreover, they exhibit recovery from induced refractive errors upon the removal of form deprivation or optical defocus, characterized by a slowdown in axial growth to return to the normal length expected for their age. Form deprivation myopia represents an open-loop condition, allowing the eyeball to continue growing, while negative lens-induced myopia ceases when the eyeball matches the focal length of the negative lens. Despite the least clarity in the squid model's characteristics, it still responds to visual signals. These phenomena provide a solid scientific foundation for the optical control of childhood myopia.[20-22]

Rodents, particularly mice, have become increasingly prevalent in myopia research. The myopic changes observed in mice exhibit characteristics similar to human myopia, such as axial elongation of the vitreous chamber.[19] The retinal structure of mice is akin to that of other mammals, featuring dichromatic vision with cones sensitive to middle and short wavelengths. While mice lack a fovea centralis, they possess a visual streak, which offers optimal visual acuity at 1.4 cycles per degree. In comparison to humans, mice have larger crystalline lenses, relatively smaller vitreous chambers, and lack the ability for lenticular accommodation.[23] Mice demonstrate stable responses to form deprivation and lens-induced defocus. Despite being nocturnal rodents, they are active during the day, emphasizing the significant impact of visual stimuli on refractive development.[24,25] Moreover, mice exhibit rapid growth throughout the year, and the technical infrastructure for experiments involving mice is relatively well established. Consequently, mice serve as a common model for studying the interplay of genetics and environmental factors in myopia and have been employed in myopia drug development.[26]

Research methods in animal studies of light on myopia

Research in myopia in animal models has a history spanning over four decades. Major research methods encompass the observation of the emmetropization process in animals, the assessment of ocular growth after inducing refractive errors, and the analysis of

ocular biometrics under additional conditions or specific environments. These biometrics included axial length, corneal curvature, anterior chamber depth, lens thickness, and vitreous chamber depth.[14] As myopia development involves changes in signaling and biomechanical properties across the retina, retinal pigment epithelium (RPE), choroid, and sclera, experimental designs aimed to investigate these tissues individually. For example, researchers observed retinal electrophysiological signals, analyzed cellular morphology in the retina and RPE, measured choroidal blood flow, studied the effects of smooth muscle contraction on choroidal thickness, examined scleral cell differentiation, extracellular matrix composition, and arrangement, as well as signaling molecules and gene expression from the retina to the choroid.[26-29]

Experimental methods involve the use of ultrasound or optical coherence tomography (OCT) to measure axial length and biometrics, electrophysiological testing to study retinal photoreceptor signaling, electron microscopy for observing tissue structure at various levels, and X-ray spectroscopy analysis or OCT angiography for understanding choroidal blood flow dynamics. In addition, techniques such as tissue immunostaining, fluorescence staining, and Western blotting are employed to localize and validate the mechanisms governing visual-guided ocular growth.[30]

In animal myopia development, decreased scleral thickness and collagen fibril diameter,[26] as well as increased crimp angle of scleral collagen fibrils were demonstrated.[27] Hyperosmolarity and decreased tissue hydration were noted in the choroid, RPE, and photoreceptor outer segments accompanying deprivation myopia.[31] However, the retina had compensatory mechanisms that allowed retinal dysfunction to be detected by electroretinogram (ERG) more prominently than the occurrence of morphological disorganization of the retina.[28]

To comprehensively grasp the cellular and molecular biology of myopia regulation, experiments also investigate changes in gene expression relevant to eye growth and refractive status within ocular tissue. Transcriptomic and proteomic datasets complemented each other in identifying pathways associated with myopia development. Retinal insulin-like growth factor 2 messenger RNA (mRNA)-binding protein 1 (Igf2 bp1) emerged as a potential biomarker for lens-induced myopia,[29] though there were differential scleral gene expression patterns in myopigenesis.[32] Differential expression of protein tyrosine phosphatase, receptor type B, transforming growth factor beta-induced (TGFBI), and basic fibroblast growth factor 2 (FGF-2) in the choroid/RPE was confirmed by real-time polymerase chain reaction.[33] The genes differentially expressed in response to defocus in marmosets retina overlapped with human myopia quantitative trait loci, suggesting potential therapeutic targets.[34] Furthermore, manipulation of the mouse genome (cone signaling pathway or hypoxia-inducible factor [HIF]-1α signaling pathway) disrupted the response of ocular growth to visual signals and may aid in the development of novel myopia treatments or drug targets.[35,36]

Research methods in clinical studies of light on myopia

Research on the relationship between myopia and light sources includes investigations into the protective effects of outdoor lighting,[37,38] retrospective analyses of violet light (VL, 360-400 nm wavelength)-filtering contact lenses and phakic intraocular lens on eye growth,[39,40] and recent clinical trials on repeated low-level red light (RLRL) therapy.[6] To establish the efficacy and safety of RLRL for myopia control, larger and longer-term randomized controlled trials are essential. In addition, investigating the rebound effect after discontinuation of RLRL is crucial. While light therapy holds potential, additional research is necessary for a comprehensive understanding of its optimal clinical application in myopia treatment.

The Effects of Light Sources Properties on Myopia

Illumination cycles and intensity

Previous animal studies have indicated that the nature of light sources can affect eyeball growth, including factors such as the day-night cycle and illumination intensity.[37,41] Light sources lacking a circadian rhythm can lead to abnormal eyeball growth due to the absence of regulation by the dopamine system. Low illumination levels have been associated with myopigenesis, whereas increased brightness can prevent myopia formation. When given dopamine receptor antagonists, the effects of low illumination levels on myopia induction in young chicks are mitigated, demonstrating the involvement of the dopamine system.[42]

Spectral wavelengths

In addition to lighting cycles and intensity, past animal experiments have also demonstrated that light sources of different wavelengths can influence eyeball growth regulation.[35,42,43] Longer wavelengths such as green or red light have been found to induce myopia in chicks, mice, fish, and guinea pigs, whereas shorter wavelengths such as blue or violet light tend to lead to hyperopia.[11,35,42-47] Longitudinal chromatic aberrations (LCAs) may play a crucial role in these variations. In other words, blue light, or shorter wavelengths, refracts more in the axial direction of the eye compared to red light, converging in

front of the retina. This may influence eye development and reduce axial elongation, whereas red light exhibited the opposite effect.[48]

Conversely, this LCA effect does not dominate the refractive status of the eye in other animal models, such as tree shrews and rhesus monkeys, where red light has been observed to have a protective effect against myopia.[49-52] This suggests that mechanisms distinct from LCA may also play a regulatory role. Animal experiments have also observed that compensation mechanisms for choroidal thickness and axial length differ under red and blue light conditions (significant changes in choroidal thickness under red light and no significant changes under blue light). This is inferred to be driven by different cone cell signal ratios.[53] In addition, infrared light (wavelength range 630–1000 nm) is also considered to have a potentially protective effect against myopia.[48]

Furthermore, the results of clinical trials indicate that outdoor activities are a crucial environmental factor in myopia control,[37,38] with evidence suggesting that adequate exposure to violet light may be beneficial for myopia.[39,40] RLRL therapy has shown promise in slowing myopia progression, as evidenced by reductions in refractive error and axial length changes. However, the limited number of studies, short follow-up duration, and variations in RLRL parameters contribute to the low certainty of the evidence.[6] Despite observed improvements in uncorrected visual acuity and choroidal thickness during treatment, the optimal RLRL protocol remains unclear.

Interaction of wavelengths and refractive state of the eye

The refractive state of the eye is another factor that may influence the relationship between light source signals and eyeball growth regulation. Some studies have investigated the effects of lens-induced refractive errors and different monochromatic lights on eye growth regulation. Experimental results in species such as chicks, guinea pigs, and mice have shown that short-wavelength violet (380 nm) and blue light (470 nm) can inhibit eye growth under lens-induced myopic defocus conditions.[35,54,55] Tree shrews, when exposed to cyan light (505 nm) under initially well-focused eyes, develop myopization and are unable to maintain emmetropia or induce hyperopia. However, when exposed to cyan light with negative-power lenses (−5D) inducing myopia, eye growth is initiated to compensate for the negative-power lens signal.[56] Rhesus monkeys' experimental results have demonstrated that red light exposure has a protective effect against myopia in both hyperopic and myopic defocus conditions.[50] These experiments collectively suggest that the focusing state of the eye (refractive error) influences the regulation mechanisms guiding eyeball growth, but the interaction between the light spectrum and species varies.

Color contrast signals

In addition to exploring the effects of monochromatic light and refractive state, the contrast generated by light sources of various wavelengths is a crucial clue in eye regulation. Researchers have proposed a possible explanation called the "opponent dual-detector spectral drive model," which suggests that cone cells responsible for receiving short-wavelength-sensitive (SWS) and long-wavelength-sensitive (LWS) light signals jointly regulate eyeball growth.[57] Experiments in chicks have observed that eye growth compensation for lens-induced myopia or hyperopia is better under white light conditions than under monochromatic light (where both red and blue light-induced less growth change). Thus, while color contrast is not a necessary condition for emmetropization, retinal physiology can utilize color contrast to regulate eyeball growth.[53] Many research findings reinforce this conclusion: the inclusion of multiple wavelengths in the visual environment is essential for the normal functioning of emmetropization mechanisms.[58-60]

Flicker status of illumination

The flicker pattern of light sources is also believed to affect eyeball growth regulation.[61-64] Moreover, the sensitivity of cone cells to contrast signals generated by color changes and brightness variations differs depending on the refractive state of the eyes. Studies have found that in chicks, guinea pigs, and mice, under myopic defocus conditions, the sensitivity of SWS cone cells and medium-wavelength-sensitive (MWS) or LWS cone cells remain relatively stable. Therefore, brightness changes become the dominant signal for eyeball growth. In contrast, under hyperopic defocus, as hyperopic defocus increases, the sensitivity of SWS cone cells increases significantly compared to MWS or LWS cone cells. Consequently, color changes become the dominant signal for eyeball growth. Experiments involving color changes (flashing illumination with reverse red/green or blue/yellow) signal the eye to grow in a myopic direction, whereas brightness fluctuations signal the eye to grow in a hyperopic direction. Furthermore, the changes in ocular length induced by color variation are much greater than those induced by brightness changes. In summary, it is inferred that the eye can distinguish between hyperopia and myopia based on changes in brightness or color and that this interaction is influenced by the eye's refractive state.[65] The effect of light properties on refractive status and the potential mechanism were summarized in Table 1.

Table 1: The effect and mechanism of light properties on ocular growth and refractive status

Light properties	Subjects	Effect on myopia development	Mechanism (reference)
Illumination cycle and intensity	Children, chicks, rhesus monkey	Light lacking a circadian rhythm disrupted eyeball growth	Dopamine system[37,41,42]
		Low illumination associated with myopigenesis; increased brightness prevented myopia formation	
Spectral wavelength			
Monochromic short wavelength	Fish, mice, guinea pigs, chicks	Lead to hyperopia	LCAs played a role, reducing axial elongation; protect from luminance change[11,35,42-44,46-48]
Monochromic long wavelength	Fish, guinea pigs, chicks	Lead to myopia	LCA as target of axial elongation[11,42,45,46,48]
	Children, tree shrews, rhesus monkeys	Observed to have a protective effect against myopia	Increased choroid thickness and reduced scleral hypoxia[6,49-52,66]
Interaction of wavelengths and refractive state	Tree shrews, guinea pigs	Cyan light (505 nm) initiated eye growth to compensate for negative-power lens signal but cannot maintain emmetropia or induced hyperopia	Emmetropization mechanism responds to multiple defocus-related cues[56]
Color contrast/ broad spectrum	Chicks, tree shrews, guinea pigs	Better eye growth compensation under white light conditions compared to monochromatic light	Opponent dual-detector spectral drive model; joint regulation by SWS and LWS cone cells[53,57-60]
Flicker status	Chicks, mice	Brightness changes signaled the eye to grow in a myopic or hyperopic direction	The sensitivity of cone cells to color/brightness contrast signals depended on the eye's refractive state[62,64,65]
		Flashing illumination (reverse red/green or blue/yellow) signaled the eye to grow in a myopic direction	

LCAs=Longitudinal chromatic aberrations, SWS=Short-wavelength-sensitive, LWS=Long-wavelength-sensitive

Signaling Molecules in Visual Input Transduction and Ocular Growth Regulation

Scholars proposed a model of visual-guided ocular growth, wherein retinal biochemical signals initiate a cascade through the RPE and choroid to regulate the synthesis and remodeling of the scleral extracellular matrix. Various signaling molecules, including dopamine,[67-69] melanopsin,[69,70] acetylcholine,[71] nitric oxide,[72,73] γ-aminobutyric acid,[74,75] ZENK,[75] nicotine,[76] opiates,[77] serotonin,[78] and insulin-like growth factor 2 mRNA-binding protein 1[29] are involved in this process.

Scleral biomechanical properties are influenced by extracellular matrix composition (collagen, proteoglycans, and glycosaminoglycans) and growth factors secreted by scleral fibroblasts, such as FGF-2,[79] TGF-β,[80] insulin,[81] and glucagon.[82] Matrix metalloproteinases (MMPs)[83] and tissue inhibitors of metalloproteinases[84] also affect scleral remodeling and axial elongation. In myopia development, MMP-2 and STAT3 are implicated, with experiments showing MMP inhibitors effectively reducing myopia progression.[84-86]

Genetic studies suggested that MMP gene variations increase myopia risk.[87,88] Scleral hypoxia, regulated by HIF-1α and HIF-2α, contributes to myopia formation by upregulating MMP-2 expression.[66,89] Despite these findings, the precise mechanisms by which light sources modulate myopia remain unclear, necessitating further research for effective myopia management strategies.

Indoor Light-emitting Diodes Lighting for Myopia Control

Animal experiments suggested that ocular development responds to color cues and multicolored white light may aid emmetropization.[37,38,42,60] Increased outdoor time slows myopia progression, potentially due to rich contrast signals from sunlight. Emerging indoor lighting technologies mimics sunlight's spectrum, with red, green, blue, and white light or red, green, cyan, warm white, and cool white light light-emitting diodes (LEDs) offering solutions to optimize nonimage-forming parameters, such as circadian action factor.[90-93] Further research on the impact of LED lighting impact on ocular growth may lead to novel myopia control strategies.

Future Research of Light on Myopia Control

Myopia research has comprised animal and epidemiologic studies and clinical trials. Animal experiments require careful consideration of the similarity of ocular structure to humans, stable responses to external stimuli, and ease of maintenance for the environment. In contrast, clinical trials necessitate comprehensive protection of child participants' safety, and the analysis of therapeutic mechanisms will be limited by the challenging acquisition of ocular specimens.

Currently, there is inconsistency in the experimental models among research teams. The reports suggested that either red or blue light could inhibit myopia,[35,43] whereas flicker status showed a different effect on ocular growth.[62,64,65] Meta-analysis was not performed in the review due to the heterogeneity of animal study designs and outcomes. Despite the recent surge in research on the use of red light for myopia control in children, the underlying regulatory mechanisms remain incompletely understood. Unlike most species, the impact of red light on myopia in humans lacks consistent conclusions.[6,43,94] Exploration of color contrast and broad-spectrum light sources in human was also limited.

Conclusion

The literature review above suggests that the properties of light sources have a significant impact on eyeball growth regulation. Factors such as light intensity, lighting cycles, spectral wavelengths, refractive state of the eye, color contrast signals, light source flicker status, variations in the evolution of cone cells across different species, and the specific myopia models used in experiments can all lead to differences in observed experimental results. Overall, previous research indicates that the nature of light sources plays a crucial role in the regulation of eyeball growth, and different light source characteristics may result in different regulatory effects. Future research may optimize experimental methods to elucidate the intricate regulatory mechanisms of light on myopia as a further target of treatment.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

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