JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2025, 76, 4, 355-367
www.jpp.krakow.pl | DOI: 10.26402/jpp.2025.4.01

Review article

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EXPERIMENTAL MODELS OF MYOPIA DEVELOPMENT: A REVIEW OF LITERATURE

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Myopia is one of the most prevalent refractive errors and one of the leading causes of visual impairment and blindness worldwide. It results from a mismatch between the axial length and optical power of the eye, resulting in a focal plane that lies in front of the retina. In children and young adults, myopia is most commonly caused by excessive elongation of the eyeball during development - a hallmark of school-age and some early-onset genetic forms of myopia. However, myopic refractive error can also result from other mechanisms, such as increased lens power in age-related nuclear cataracts or corneal steepening in keratoconus, which are not associated with axial elongation. The prevalence of myopia in young Asian adults has increased from 20–30% to 80–85% over the last 50 years. In contrast, recent meta-analytic data for European young adults, emphasizing studies with cycloplegic refraction essential for accuracy, indicate myopia prevalence rates of approximately 19–24%. The prevalence of high myopia (greater than or equal to –6.0 diopters) has increased disproportionately to myopia in the last 50 years, from 1–5% to 10–20% and became a global problem. The reason for this state of affairs is believed to be lifestyle and prolonged near vision activities. Although refractive error can be corrected, sight-threatening pathologies such as retinal detachment, macular degeneration, glaucoma, and cataracts are more challenging to control. Owing to years of research, the biological mechanisms of eye growth and refractive development are increasingly elucidated. The signaling cascade mechanisms that link the retinal image processing and alterations in choroidal thickness and scleral development have also been studied. While the retina can detect defocus and changes in defocus, decades of research have led to a growing understanding of the fundamental pathways in visually guided eye growth, yet the precise initial mechanisms by which the retina senses and transduces these optical signals continue to be an active and important area of investigation. Animal studies have demonstrated that the retina can locally regulate visually guided eye growth through intrinsic mechanisms, even in the absence of direct input from the brain. The precise molecular mechanisms underlying common forms of myopia, particularly those involving axial elongation, are yet to be fully elucidated. This reflects the complexity and multifactorial influences inherent even in these prevalent forms, alongside the challenges posed by experimental models in completely recapitulating all aspects of the human condition.

Key words: *myopia, retinal defocus, axial elongation, dopamine, retina, visual deprivation, ocular growth, choroid, microRNA, muscarinic antagonists*

PHYSIOLOGICAL AND BIOCHEMICAL MECHANISMS OF MYOPIA DEVELOPMENT

Studies using a range of animal models, from primates to chicks and rodents, have helped establish core mechanisms of emmetropization and myopia development. The main directions to pay attention to are visual signals causing retinal defocus, which are responsible for guiding eye development and emmetropization. By manipulating applied retinal defocus, it is possible to affect the development and refractive errors of the eye. In a normally developing eye, hyperopic defocus triggers biochemical signals that stimulate axial elongation, whereas myopic defocus suppresses eye growth (1). Originating in the neuroretina, this signaling is relayed and actively modulated by the retinal pigment epithelium (RPE) and choroid, leading to widespread structural remodeling that, while most critically affecting the sclera to alter axial length, also involves changes in the neuroretina, RPE, and choroid themselves. Disruption or misinterpretation of these retinal defocus cues can impair this feedback loop, leading to persistent axial elongation (myopia) or insufficient growth (hyperopia) (2-4). In addition to empirical evidence from animal and molecular studies, theoretical frameworks have offered valuable insights into

the control of eye growth. Hung and colleagues proposed the Incremental Retinal-Defocus Theory (5) and later expanded it into a unifying model (6), both of which conceptualize emmetropization as a feedback-regulated process driven by retinal defocus. These models, supported by schematic analysis and computer simulation, describe how defocus signals may incrementally influence axial elongation.

Visually controlled alterations in eye development have the greatest impact on the eyes of juvenile animals, although older animals can also experience compensatory adjustments (7-9). Also, signals responsible for guiding eye growth are locally processed. Even a severed optic nerve does not prohibit defocus compensation. Limiting defocus to local retinal areas leads to regional eye growth alterations. Localized regions of the peripheral retina, particularly in the nasal, temporal, and inferior quadrants, have been shown to independently regulate ocular growth when exposed to defocused or form-deprived visual input. These regional responses can lead to sectoral changes in axial elongation that collectively influence central refractive development (8, 10, 11). Growth induced by light defocus always involves changes in extracellular matrix of the sclera and scleral biomechanical properties (12).

Changes in the choroidal thickness were also observed (13). The choroid has an active role in the visual control of eye development and refraction, as a part of the compensatory response reaction to induced defocus and may affect emmetropization and eye development as an accommodating response (14, 15).

Either through cellular processes that do not require accommodation or ciliary muscle activity, as well as potential muscarinic and nonmuscarinic activities, atropine impacts eye development and prevents induced myopia (2). There are several biochemical substances involved in the regulation of eye growth. List consists of, but it is not limited to retinal dopamine or retinoic acid. A cascade of cell signals originating from the retina that affect scleral biochemistry and control eye development may exist, according to various changes in the retina, RPE, choroid, and sclera. Molecular changes in gene expression in those structures suggest that the retina uses separate routes to signal myopic and hyperopic defocus for eye development.

Decades of research utilizing diverse animal experimental models have firmly established that visual feedback is paramount in guiding refractive development and overall eye growth. These models have been crucial for identifying key mechanistic links between visual experience, environmental inputs, and genetic factors, and for delineating the complex regulatory pathways that govern ocular growth, emmetropization, and the progression of myopia.

Myopia can develop as an adaptation to environmental visual scenarios via emmetropization processes, but it can also advance due to a combination of visual conditions and genetic variables that alter the operation of visually led eye development control mechanisms.

ANIMAL MODELS MOST OFTEN USED IN EMMETROPIZATION AND MYOPIA STUDIES

The term ‘emmetropization’ is often broadly used in the literature to describe the visually guided process of refractive development, where the eye adapts its components to achieve focused vision during growth (2). However, the concept and its precise target endpoint have been subjects of considerable discussion. As Rozema *et al.* note, ‘emmetropization’ is sometimes considered a source of ambiguity as it can suggest a mechanism targeting a precise zero refractive error (0 D, or perfect emmetropia) (16). Yet, this traditional interpretation is debated, as evidence from human epidemiological data and comparative studies indicates that the developmental process often stabilizes at a state of low hyperopia (*e.g.*, +0.50 D to +1.00 D under cycloplegia) rather than absolute emmetropia (16). Understanding these nuances in the goals and outcomes of visually guided eye growth, including whether the target is non-cycloplegic emmetropia or a specific cycloplegic refractive state, is important when evaluating experimental models and their relevance to human myopia. Animal studies remain crucial for dissecting the active, visually guided mechanisms involved in these refractive adaptations. Visual input is a key modulator of postnatal ocular growth, and in many investigated species, this process generally guides the eye towards emmetropia (2, 16, 17). However, the outcomes and effectiveness of emmetropization can vary between species and even among different genetic strains within a species, for instance, studies in mice have documented that while some strains develop emmetropia or myopia, others exhibit a natural tendency towards hyperopia under normal visual conditions (18). Despite these variations, the fundamental principles of visually guided eye growth appear to be broadly conserved.

Myopia can be experimentally induced in animal models by introducing negative (concave) lenses in front of the eye, and hyperopia can be analogically induced by adding positive (convex) lenses (19-22). Beyond lens-induced and form-deprivation models, several alternative experimental approaches have been developed to investigate the mechanisms of refractive development. Manipulation of longitudinal chromatic aberration (LCA) through narrow-band lighting has demonstrated that spectral cues can influence refractive development, with long-wavelength (red) light exposure promoting hyperopia and attenuating myopia progression in animal models (23, 24). Additionally, differential stimulation of retinal ON and OFF pathways has been shown to affect eye growth, suggesting that contrast polarity and luminance processing play significant roles in refractive development (25). Dark rearing experiments have revealed that the absence of visual stimuli can disrupt normal ocular growth patterns, leading to myopic shifts (26, 27). Furthermore, variations in ambient light intensity have been found to modulate retinal dopamine release, with higher light levels exerting a protective effect against myopia by inhibiting excessive axial elongation (28). Collectively, these methodologies provide valuable insights into the complex interplay between environmental factors and ocular growth regulation. In a wide range of diverse species, including invertebrates and primates, experimental models of myopia and the visual regulation of eye growth have been investigated. These species include macaque (27), marmoset monkey (29), tree shrew (7), chicken (30), guinea pig (31), mouse (32), fish (26), and squid (33). With the exception of squid, all of these species have been demonstrated to exhibit myopia in response to visual form deprivation, compensation for optically imposed myopic and hyperopic defocus by regulating axial length, and recovery from the induced refractive error when form deprivation or optical defocus has been finally removed. Despite having the least amount of data, the squid model responded to controlled alteration of the visual environment, changing its growth when focus was improved: Turnbull *et al.* achieved this by using inherent longitudinal chromatic aberration (LCA) to create varied focal lengths within the squid eyes (33). These findings suggest that visual regulation of eye growth is a fundamental characteristic of the camera-type eye, potentially having evolved independently in different lineages. Despite substantial differences in ecology, ocular anatomy, visual function, and visual acuity, diverse species, including both vertebrates and invertebrates, exhibit visually guided eye

growth, indicating that key regulatory mechanisms are broadly conserved. Each species offers distinct advantages for studying the mechanisms of visually guided eye growth and important signaling pathways that control refractive eye development across species from an experimental standpoint; however, physiological and anatomical differences must be taken into consideration when trying to extrapolate findings to humans (21). Although there are notable differences across species, the overall cellular architecture of the retina and the neural signaling circuitry are generally similar among vertebrates (34, 35). While some species may be multifoveal or have an area centralis or visual streak, which are retinal areas with higher photoreceptor and ganglion cell density, diurnal primates, like humans, have a single fovea responsible for high visual acuity perception (36-38). The retinal vascular structure and the visual photopigment types that allow color perception differ between animals (38-41). The retinas of the most popular experimental species are compared and contrasted in *Table 1*, based on their anatomical similarities and differences.

Significant interspecies differences exist in the mechanisms of accommodation, which control the eye's ability to focus and may potentially contribute to the development of myopia through its impact on retinal defocus. In many species, including humans, accommodation is accomplished by altering the crystalline lens power by contracting the ciliary muscle, however in some other species (fishes), accommodation is accomplished by moving the lens backward and forward (42, 43). It has also been noted that some animals' (chicks) eyes have the ability to change corneal powers (30, 44, 45).

The first report of experimental myopia induction was published by Wiesel and Raviola (46), who used lid fusion in monkeys and demonstrated that this form of early vision impairment led to a myopic shift in refractive state and axial elongation. Myopia can be induced by the form-deprivation myopia (FDM) models, or using, for example, negative lenses (lens-induced myopia, LIM) (47) or by creating genetically modified animals (48). When compared to form-deprivation, lens-induced myopia (LIM) produces a more pronounced myopic shift and greater axial elongation in mice, as demonstrated by Barathi *et al.* (47) using –10 D spectacle lenses. Meanwhile in terms of the degree of myopia, axial length, and pathological changes, the FDM and LIM models did not significantly vary from one another, in the guinea pig model (31). *Table 2* represents comparison of two commonly used paradigms for experimental myopia induction (49).

The guinea pig serves as a valuable and widely used model for experimental myopia. Xiao *et al.* (31) emphasize its utility due to a strong sensitivity to both form-deprivation and lens-induction methods, making it a highly responsive and effective model for studying myopia induction. It is also worth noting that Xiao *et al.* suggest primates are generally considered the most ideal models for human myopia, given their greater similarities in ocular anatomy and physiology (31).

RETINAL MODULATORS OF OCULAR GROWTH

Numerous research studies have been conducted on retinal neurotransmitters, including dopamine, acetylcholine, insulin and glucagon, to determine their role in the regulation of ocular growth (50-52).

The primary catecholamine present in the retina is dopamine. The dopaminergic amacrine and interplexiform cells are responsible for producing and releasing this neurotransmitter (53). Dopaminergic amacrine cells (DACs), which are irregularly distributed throughout the retina, produce and release retinal dopamine (53). Several types of postsynaptic receptors can be activated by dopamine through local synaptic release from DAC

Table 1. Retinal differences in species used for myopia models (UV, ultraviolet; S, short wavelength; M, medium wavelength; L, long wavelength) (29, 72, 82, 148-170).

Species	**Central Retinal Thickness**	**Photoreceptor Types**	**Peak Sensivivities of Photoreceptor Class**	**High Cell Density Region**
Human	182 μm at fovea[148]	Rods, Cones	S (419 nm), M (531 nm), L (558 nm) [150]	Fovea (38,000 ganglion cells/mm^2)[151]
Rhesus (Macaca mulatta)	207 μm[152]	Rods, Cones	S (440 nm), M (536 nm), L (565 nm)[153, 154]	Fovea (33,000 ganglion cells/mm^2)[155]
Marmoset	230 μm[29]	Rods, Cones	M/L (543, 556, 563 nm)[156]	Fovea[29]
Tree shrew	213 μm[72]	Rods, Cones	S (428 nm), L (555 nm)[157]	Area centralis[158]
Guinea pig	150 μm[159]	Rods, Cones	S (429 nm), M (529 nm)[160]	Visual streak (2,272 cells/mm^2)[161]
Mouse	202 μm[162]	Rods, Cones	UV (370 nm), M (505 nm)[163]	Visual streak (6,000 ganglion cells/mm^2)[162]
Chick	295–350 μm at area centralis[82,164]	Rods, Cones	S1 (415 nm), S2 (455 nm), M (508 nm), L (571 nm)[165]	Area centralis (24,000 ganglion cells/mm^2)[166]
Fish (Zebrafish)	191 μm[167]	Rods, Cones	UV (361 nm), S (411 nm), M1 (482 nm), M2 (503 nm), L (565 nm)[168]	Area centralis (37,000 ganglion cells/mm^2)[169]
Fish (Tilapia)	200 μm[170]	Rods, Cones	S1 (380–420 nm), S2 (440–480 nm), M/L (500–600 nm), and (600–800 nm)[149]	No data

(54) or extra-synaptically through paracrine diffusion across the retina (55). The fluctuations seen in the metabolites of the dopaminergic pathway during experimentally generated changes in eye growth and refractive condition, as well as the effects of dopaminergic drugs on experimentally induced myopia, have suggested that dopamine plays an important role in the regulation of ocular growth (50, 51, 53, 56). The amount of light reaching the retina has a significant impact on dopamine release, which follows a diurnal cycle with high release during the day and reduced release at night (57, 58). This rhythm is predominantly light driven in the chick, with a small circadian component (57, 58). By regulating cell coupling and modulating retinal diurnal cycles, dopamine is believed to play a neuromodulatory role in light adaptation (53, 57). Ocular growth regulation has been linked to the dopaminergic system as demonstrated in *Fig. 1*. In chicks, rhesus monkeys, guinea pigs, and tree shrews, retinal dopamine is downregulated throughout increased ocular growth (59-62). Diffusers or negative lenses may reduce metabolism and release of dopamine in individuals with FDM and LIM, according to medium-term alterations in the rate of dopamine synthesis, turnover, dopamine, and 3,4-dihydroxyphenylacetic acid (DOPAC), a metabolite of dopamine (56). Researchers have demonstrated that in eyes developing form-deprivation myopia (FDM), vitreal DOPAC levels still rise in response to light exposure, but the amplitude of this increase is significantly attenuated compared to non-deprived eyes, indicating a reduced but not absent dopaminergic response (63). This shows that the dopamine release is reduced very quickly and then remains steady.

The ultimate question is whether the decrease in dopamine release is a cause or consequence of the increased rate of eye growth. Dopamine receptor agonists supplementation stops the abnormal axial elongation in both FDM as well as LIM (61). However, according to a recent analysis, in guinea pigs, progression of axial elongation in LIM seems to be more dopamine independent (61). Myopia occurrence may be lower in children who spend more time outside (64) due to light-induced alterations in dopamine production. In experimental studies, the production of retinal dopamine, light intensity, and decreased myopia rate in chicks are correlated, which gives support to this hypothesis (65).

Another recent study on chicks mentioned the importance of light exposure on dopamine elevation. After 30 minutes in white light (430–630 nm, 468 lux), retinal dopamine and vitreal DOPAC concentrations were significantly higher, when compared to chicks kept in the dark. Comparatively to the other eyes with black occluders, vitreal DOPAC was also elevated after exposure to red, blue or UV light (14).

Acetylcholine (ACh) plays an important role in retinal development and may be involved in the regulation of ocular growth. It is synthesized and released by cholinergic amacrine cells and has been found to influence visual processing and cell signaling in the retina (66). Studies suggest that ACh may contribute to visual regulation of eye growth and myopia development through its modulation of retinal signaling pathways (52).

ACh receptors are represented by two major groups of membrane receptors, ionotropic nicotinic acetylcholine receptors (nAChR) and metabotropic muscarinic acetylcholine receptors (mAChRs) (67). Acetylcholine appears to be vital in the development of the retina (66). Currently, there is strong evidence that acetylcholine regulates eye growth by acting on both muscarinic (mAChR) and nicotinic receptors (nAChR) (68). There have been consistent reports of the anti-myopic effects of muscarinic receptor antagonists (like atropine) in the animal models tested in this context, which include the mouse (69), guinea pig (70), chick (71), tree shrew (72), and monkey (46, 59). Atropine injected intravitreally was reported to prevent the progression of lens-induced and form-deprivation myopia in chicks (71). Recent theoretical models, such as the Incremental Retinal-Defocus Theory (IRDT), highlight dopamine's pivotal role in ocular growth regulation. According to IRDT, sustained retinal defocus diminishes dopamine release from amacrine and interplexiform cells, leading to decreased proteoglycan synthesis and compromised scleral structure, thereby promoting axial elongation and myopia development (5). Expanding on this, Hung *et al.* (6) developed a computational model integrating genetically pre-programmed signaling with blur feedback mechanisms, demonstrating how variations in dopamine-mediated pathways can influence refractive outcomes. These models underscore the significance of dopamine as a neuromodulator in the

Table 2. Comparison of two commonly used paradigms for experimental myopia induction (49).

Method	**Form-Deprivation Myopia**	**Lens-Induced Myopia**
Mechanism	Coverage of the eye (typically frosted diffuser or by suturing the eyelids closed)	Minus power lens placed in front of the eye
Similarities	• Reduction in dopamine release • Reduction in retinal expression of immediate early gene Egr-1, reversible by dopamine agonists injection • Choroidal thinning • Scleral growth • Inhibition possible to achieve by atropine injection	
Differences	• No defined endpoint (open-loop condition) • Predomination of D2 receptor mechanism in inhibitory effect of dopamine and acetylcholine • Severly retarded by exposure to bright light	• Excessive growth ceased when stimulus in neutralized (closed-loop condition) • Both D1 and D2 receptors are engaged • Only slowed down by bright light exposure

emmetropization process and its potential as a therapeutic target in myopia control strategies (6). Myopia development has also been shown to be inhibited by more specific antimuscarinic agents, like pirenzepine and himbacine (60, 73).

Similar to its systemic role, retinal insulin has opposite effects to glucagon. Insulin enhances the proliferation of neural progenitor cells in the ciliary marginal zone of the postnatal chick retina, whereas glucagon reduces this proliferation (74, 75). These neural stem cells multiply more quickly as a result of form deprivation, which also lengthens the eyes. Insulin has been found to regulate ganglion cell formation and their regeneration following toxin-induced cell loss (76). Glucagon might play a role in the detection of defocus, at least in chicks. Feldkaemper *et al.* conducted a study where chicks were given intravitreal injections of saline or various doses of insulin while wearing positive or negative lenses (77). Authors evaluated corneal curvature, axial length, and refractive error. Injections of insulin (0.3 nmol) in control chicks group slightly shifted refraction towards myopia. Insulin injections (0.3; 0.03 nmol) prevented hyperopia when plus lenses were used by significantly increasing axial elongation and inducing myopia. Intravitreal glucagon injections in chicks have been shown to slow down the axial elongation normally induced by negative lenses, suggesting that glucagon actively opposes myopiagenic stimuli (78). Additionally, lens-induced myopia was observed to be worse in insulin presence. An increase in anterior chamber depth and thickening of the crystalline lens were the main features associated with axial elongation. The levels of vitreal glucose were temporarily lowered by insulin. Insulin also increased the content of mRNA for retinal transcription factor ZENK, while decreasing the number of ZENK-immunoreactive glucagon amacrine cells is frequently associated with the progression of myopia (77). Glucagon treatment promotes choroidal thickening and alters the expression of genes associated with ocular growth, including the retinal transcription factor ZENK (77). Insulin also appeared to modulate choroidal thickness through an RPE-dependent mechanism, as demonstrated *in vitro* using chick eyecup preparations, where choroidal thinning occurred in the presence of RPE or RPE-conditioned medium (78, 79).

LOCAL OCULAR ENVIRONMENT AND MYOPIA DEVELOPMENT

Local ocular mechanisms seem to play a significant role in regulating ocular growth (80). Studies on animals have shown that visually guided refractive development is accompanied by changes in gene and protein expression across the various levels of the ocular fundus. Postnatal eye growth has been shown to be mostly regulated by local mechanisms. According to evidence from lesioning research, including optic nerve sections and corresponding pharmaceutical studies, myopia can still be induced by certain experimental manipulations in both guinea pigs and chickens even when the retina-brain connection is interrupted (81, 82). Findings from optic nerve section studies indicate that the brain plays a limited role in the precise regulation of postnatal ocular growth. In both chicks and guinea pig, eyes with severed optic nerves consistently regulate axial elongation, suggesting that growth adjustments are guided locally by the retina (83, 84). It also explains findings of localized ocular morphology changes due to localized modification of retinal responsiveness (80). While ocular growth can be regulated locally through retina to sclera signaling, central visual pathways remain relevant in the broader context of myopia control. Brain-regulated functions such as accommodation, attention, circadian timing, and light adaptation influence the retinal image quality and thus the visual signals that guide eye growth (85).

The retinal pigment epithelium (RPE) and choroid's critical placements make them plausible conduits for conveying growth regulation signals from the retina to the sclera, which ultimately affects eye size and shape. Since RPE cells are polarized and have asymmetric distributions of specific transport proteins and channels throughout their basolateral and apical membranes, they can strictly control the exchange of various molecules between the retina and the choroid, including ions, nutrients, water, and waste products (86). RPE is now recognized as a significant source of cytokines and growth factors, playing crucial functions in preserving retinal integrity, establishing the eye's immunological privilege, and possibly regulating early eye growth (86). The RPE of animals with experimentally induced myopia undergoes morphological changes (87). In form-deprived chick eyes, an increase in the total area of the RPE layer in their myopic eyes was shown to be associated with an increase of the surface area of individual RPE cells. This morphological change occurred as an adaptation to the enlarged vitreous chamber to maintain its coverage. RPE cells in the form-deprived eyes preserved their normal, hexagonal shapes while having larger surface areas (88). In the lid-suture myopia model, the RPE of the quokka wallaby showed enlarged cells, but no signs of cell count change, despite the distribution of multinucleated RPE cells being substantially affected (88). Ion and fluid transport through the RPE may be related to the regulation of eye growth based on studies of early, rapid changes

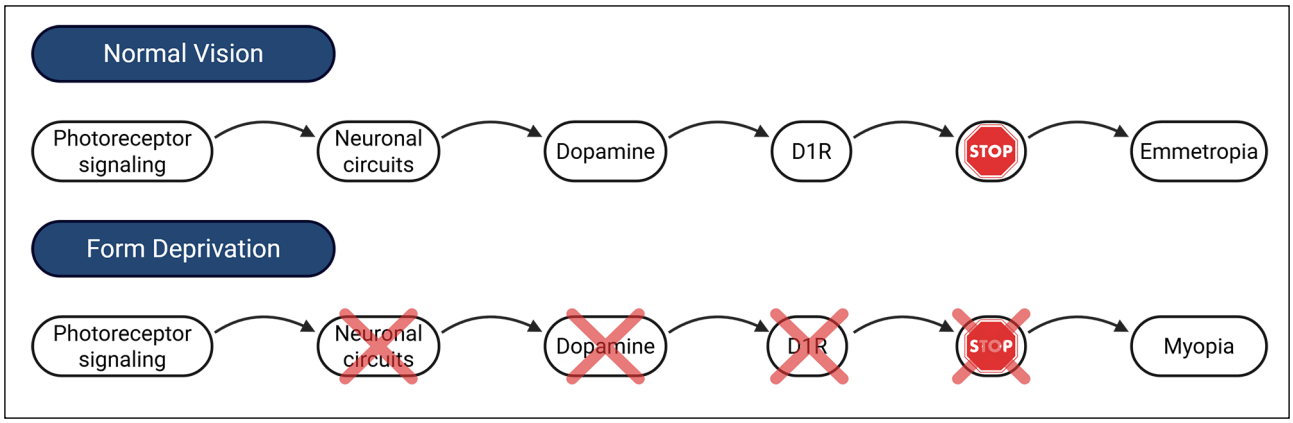

Fig. 1. Proposed mechanism by which form deprivation induces myopia via impaired dopamine D1 receptor 'stop' signaling in the retina. Reduced photoreceptor activity diminishes dopamine release and promotes axial elongation (147).

in choroidal thickness throughout the development of hyperopia and myopia in chicks (89).

The delivery of oxygen and nutrients to the outer retina, light absorption (melanin), thermoregulation, and adjustment of intraocular pressure has historically been listed as the choroid's primary roles (3). Yet, current research also suggests that the choroid has a role in regulating eye development and ocular focus adjustment, guiding the eye toward a balanced refractive state. These functions of the RPE and choroid are consistent with integrative models of eye growth, such as the Incremental Retinal-Defocus Theory, which posit that these layers transmit defocus-related biochemical signals - modulated by dopaminergic activit - toward the sclera to influence ocular elongation (5, 6). This raises the prospect of new treatment strategies for the management of myopia. The first step is to clarify the underlying signal routes and processes (3). Changes in choroidal thickness in response to forced defocus, also known as choroidal accommodation, were initially observed in young chicks (89, 90). They also exhibit the most pronounced alterations of all the tested animals (3). The retina is moved towards the new plane of focus by these alterations. As a result, while young chicks have choroids that are roughly 250 μm thick in the center and 100 μm thick on the periphery, similar to other mammals, including primates, the choroid of the chick eye increases its thickness significantly in response to significant imposed myopic defocus, causing a correspondingly large, compensatory change in refraction (3, 89, 90, 91). In response to induced hyperopic defocus, the choroid thins rather than thickens, forcing the retina towards the modified picture plane. In addition to causing myopia, form deprivation also results in choroidal thinning. However in this case, the adjustment to the location of the retina plays no compensating function. These changes in choroidal thickness happen extremely quickly, and in young chicks, high-frequency ultrasonography may pick them up in just a few minutes (80, 89, 92, 93). Guinea pigs (94), marmosets (13), macaques (95), and most recently, humans (96), have all had similar choroidal responses recorded, although in each instance the extent of the alterations is considerably lower than that seen in chicks (3, 97). These findings are summarized in *Fig. 2*, which illustrates the role of the choroid in visually guided eye growth.

During the process of myopia development, the sclera thins, particularly at the posterior pole (4, 98). According to animal models of high myopia, scleral remodeling, which is dependent on changes in the composition of the scleral extracellular matrix (ECM), plays an important role in scleral thinning (99, 100). As myopia progresses, scleral collagen accumulation decreases and its breakdown rises (101). In addition to alterations in scleral collagen, scleral proteoglycans production is reduced (102). As a result, the assembly of scleral fibrils becomes disordered, and the biomechanical aspect of the sclera weakens (103).

Evidence suggests that retinoic acid, which is a powerful inhibitor of the synthesis of scleral glycosaminoglycans, has an impact on the visual modulation and scleral remodeling in chick (104). Moreover, the increase in the rate of retinoic acid synthesis in primates' eyes may be the cause of the shown reduction in scleral galactosaminogalactan formation rates (105). Li *et al.* demonstrated that all-trans retinoic acid regulates extracellular matrix remodelling by increasing fibulin-1 and decreasing aggrecan expression in *ex vivo* guinea pig sclera and cultured human scleral fibroblasts (106). In their study, Zou and his team (70) showed that when compared to healthy and control eyes, the eyes of subjects with FDM showed the most significant alterations in refraction, axial length, and scleral remodeling, which are indicative of myopia. Hematoxylin-eosin staining demonstrated that the scleral thickness in the posterior pole area of FDM eyes was noticeably lower than that of normal eyes. In comparison to the healthy eyes, the FDM eyes exhibited a statistically significant reduction in both the amount of mRNA and protein expression of the posterior scleral collagen type I.

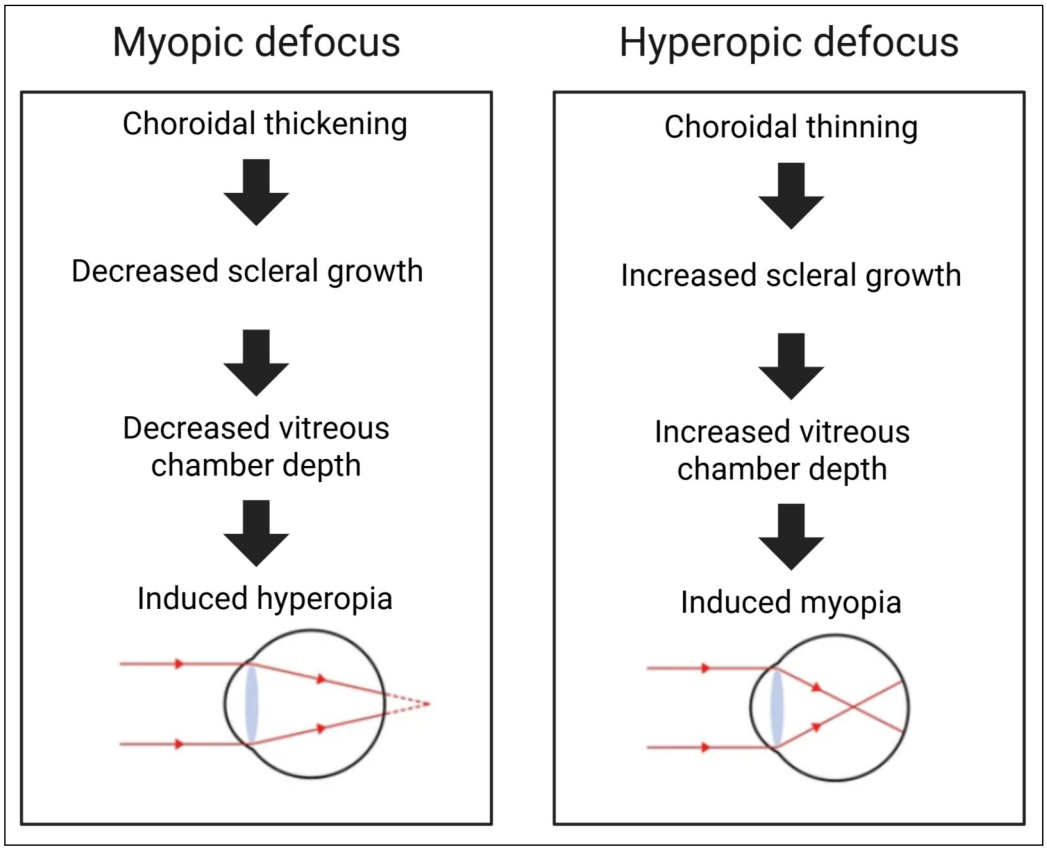

Fig. 2. The role of choroid in visually guided eye growth (86).

Moreover, the levels of mRNA and protein expression in the sclera of the FDM eyes were found to be elevated (70). There is limited evidence regarding the ionic composition of the vitreous in relation to myopia. It has been shown that in form-deprived myopic chick eyes, vitreous chloride (Cl^-) levels were elevated, while phosphate (PO_4^{3-}) and potassium (K^+) levels were reduced when compared to controls (107).

GENETIC AND MOLECULAR ASPECTS OF MYOPIA DEVELOPMENT

While familial patterns in myopia have long suggested underlying genetic predispositions, the development of myopia is now understood as a complex, multifactorial process where genetic factors interact significantly with environmental influences (108, 109). The dramatic shifts in myopia prevalence observed globally, particularly in East Asia where rates have surged in populations often without a strong parental history of myopia, underscore the potent role of environmental exposures in driving the myopic phenotype (110, 111). Therefore, contemporary genetic research in myopia focuses not only on identifying susceptibility genes and loci through approaches like genome-wide association studies (GWAS) and analysis of candidate genes in experimental models, but also on understanding the intricate gene-environment interactions that ultimately determine an individual's refractive outcome (109).

Scleral growth in hyperopes, emmetropes, and myopes is affected by genes expressed in the retina, RPE, choroid, and sclera. Aberrant expression of these genes may lead to the development of myopia and contribute to increased axial elongation (112). There are connections involving myopia and polymorphisms within sclera-associated TGFB2 gene (113), followed by verification, that the TGFB2 gene was positively related to axial length of the globe (114).

Drawing upon findings from form-deprivation studies in species such as chicks, mice, and rhesus macaque monkeys, Schippert *et al.* (115) established the first knock-out mouse model to investigate relative myopia. This model focused on the immediate early gene transcription factor ZENK (also known as Egr-1). It was observed that ZENK expression in retinal amacrine cells increased when positive lenses were used to inhibit axial eye growth, whereas its expression decreased when negative lenses amplified axial elongation. These findings pointed to ZENK's involvement in a signaling pathway that normally suppresses eye growth. Supporting this, ZENK knockout mice, compared to their heterozygous and wild-type counterparts with an identical genetic background, exhibited longer eyes and a myopic shift in refraction (115). Studies conducted on the RPE have shown that BMPs exhibit bidirectional regulation during the process of ocular growth (93, 116).

In recent years, increased interest in the role of microRNAs (miRNAs) has been observed. MiR-214, let-7c, let-7e, miR-103, miR-107, and miR-98 expression was elevated in the fetal sclera (117). In the same study, microRNA expression profiles were comprehensively cataloged in both adult and fetal human sclera, revealing a clear pattern of age-related differential regulation. Several miRNAs, including those from the let-7 family as well as miR-214, miR-107, and miR-98, were significantly upregulated in fetal sclera compared to adult tissue. These findings suggest that miRNAs may regulate extracellular matrix genes involved in collagen remodeling, thus contributing to ocular growth and potentially playing a role in the development of myopia (117). According to Chen *et al.* (118), miR-328 may influence the development of myopia by controlling the PAX6 gene, which has the impact of downregulating collagen I and integrin β1 expression while upregulating MMP-2 levels in scleral cells. Nevertheless, another study has found that even though the miR-328 expression was raised in the myopia group compared to the control group in high myopic eyes' aqueous humor, the difference between the two groups was not statistically significant (119).

In mice eyes subjected to form deprivation, it was discovered that let-7 class miRNAs were upregulated (120). Mei *et al.* (121) filtered out eight highly elevated miRNAs in FDM, including miR-294, miR-16-1, miR-466h-5p, miR-466j, miR-15a, miR-466c-5p, miR-669e and miR-468. The reduction in MMP-2 secretion by scleral fibroblasts and RPE cells in cells transfected with the miR-29a mimics was shown by Zhang in cells (122). In the future, a novel medication to slow the progression of myopia is anticipated to be based on miRNAs (4).

Barathi *et al.* (123) found that mice without the Chrm2 gene-encoded M2 receptor are less sensitive to experimental myopia induction than wild-type mice and animals lacking the M1, M4, or M5 subtypes. It was also shown that M3 receptor mutants were mostly resistant to the development of myopia. Comparing M2 knockout mice to wild-type mice, these animals exhibit greater quantities of type I collagen and lower levels of type V collagen in sclera (123).

The integration of various -omics technologies has begun to unravel the complex molecular tapestry underlying myopia development, pointing towards interconnected signaling pathways and potential biomarkers. These approaches move beyond single gene analyses to provide a more holistic view of the cellular responses to myopia-inducing stimuli.

Tedja *et al.* (124) performed a genome-wide association meta-analysis that highlights light-induced signaling as a driving force in refractive error development. Their study implicates multiple genes within signaling pathways, particularly those modulating retinal neurotransmission and circadian regulation, that are sensitive to ambient light levels. These findings suggest that retinal processing of light influences ocular growth and, consequently, myopia progression (124). A key insight emerging from transcriptomic studies is the identification of dynamic and often distinct signaling pathways activated by different visual cues. For example, Tkatchenko *et al.* (125) explored how optical defocus of opposite signs triggers bidirectional gene regulation in the retina. Their study demonstrates that gene expression profiles differ based on whether the defocus is myopic or hyperopic, implying that distinct molecular networks modulate compensatory growth responses. Transcriptomic analysis revealed that myopic and hyperopic defocus activate largely distinct retinal signaling pathways: myopic defocus was associated with the regulation of Notch, mTOR, JAK/STAT, Ephrin B, glutamate, and CREB signaling, while hyperopic defocus predominantly influenced pathways such as dopamine-DARPP32, calcium, HIPPO, G-protein-coupled receptor, TNFR1, and cAMP signaling (125). Further investigations have identified novel genes and genetic networks that regulate refractive development (18).

Complementing these findings, a 2024 meta-analysis of retinal transcriptome profiling from various animal models of myopia consistently highlighted the involvement of broader pathways, including TGF-beta signaling and those regulating circadian rhythms, suggesting common underlying mechanisms across different experimental setups (126).

Beyond direct gene expression, miRNAs add another layer of regulatory complexity. Additional insight comes from another paper, where total of 53 miRNAs were identified as differentially expressed in the retina during form-deprivation myopia, with 37 upregulated and 16 downregulated. These changes were not observed in the sclera. Analysis revealed 135 mRNA targets for 21 of the differentially expressed miRNAs, suggesting complex regulatory networks involved in ocular

growth and refractive development. The study identified nine overlapping miRNA-mRNA signaling pathways, with miR-145-5p and miR-200b-3p serving as central regulatory hubs (127). Further downstream, proteomic and metabolomic analyses are providing crucial insights into functional changes and the metabolic state of ocular tissues during myopia, and are proving particularly valuable in the search for biomarkers. A recent review has emphasized the promise of biomarkers (including metabolites and genes) for the diagnosis, prognosis, and even treatment of myopia (128). Recent work by Ji *et al.* (129) has shown that the modified LIM model was efficient, inducing a significant myopic shift (~8 D) in mice after 4 weeks. Transcriptomic and proteomic analyses identified 175 differentially expressed genes and 646 proteins, with limited correlation between the datasets. Notably, Igf2bp1 emerged as a potential LIM biomarker, validated by Western blot. Despite low mRNA-protein concordance, both omics approaches converged on KEGG pathways, particularly involving metabolic processes and disease-related pathways linked to LIM development (129). The significance of metabolic reprogramming is strongly supported by metabolomic studies. For instance, retinal metabolite levels were compared by Yang *et al.* (130). Metabolomic profiling of guinea pig retinas undergoing form-deprivation myopia revealed significant time-dependent alterations in metabolic pathways. Early changes included increased glucose accumulation and reductions in amino acids such as threonine, valine, isoleucine and tyrosine, while later stages showed lipid level downregulation. These findings indicate a metabolic shift toward energy conservation and impaired fatty acid metabolism during myopia progression. The study highlights the involvement of retinal energy and lipid metabolism in axial elongation, suggesting that metabolic dysregulation may contribute to the development of myopia and offer potential targets for therapeutic intervention (130). This aligns with broader reviews, such as one in the *International Journal of Biological Sciences*, which discuss how molecular changes in intraocular fluids are reflecting alterations in scleral remodeling, oxidative stress, inflammation, and metabolism are increasingly informative for understanding myopia (131). The power of combining these approaches is further highlighted by recent multi-omics studies, such as one by He *et al.* (132) which linked specific genetic variants (*e.g.*, in NFE2L3) to molecular changes in the choroidal vasculature relevant to high myopia.

Integrated-omics technologies are increasingly clarifying the complex molecular events in myopia. These studies identify key signaling pathways (such as those involved in light responses, cellular metabolism, and growth regulation) and pinpoint potential biomarkers like Igf2bp1 and specific miRNAs. While challenges remain, the combined insights from transcriptomics, proteomics, and metabolomics offer a potent strategy for deeper understanding and, ultimately, improved management of myopia.

MUSCARINIC ANTAGONISTS FOR MYOPIA CONTROL

Pharmacologically, atropine functions as a reversible competitive antagonist with an affinity for all five subtypes of cholinergic muscarinic receptors (MRs) - (MR1-MR5), and it has been assumed that this affinity is the primary mechanism by which atropine exerts its myopia-preventive action (133). Atropine has been found to be effective in preventing the development of myopia and shortening axial length of the eyeball (123, 134). Although atropine is traditionally known as a cycloplegic, its effectiveness in controlling myopia does not appear to rely on accommodation paralysis. McBrien *et al.* (135) demonstrated that atropine inhibited axial elongation in form-deprived chicks without affecting accommodation or pupillary responses, indicating a non-accommodative mechanism. The effect is likely exerted through muscarinic receptors in the retina, implicating retinal signaling in growth modulation (135). Atropine receptor blockade can control the expression of muscarinic receptors in the mouse animal model, which promotes scleral remodeling by encouraging the proliferation of scleral fibroblasts (69). In an *in vitro* study, atropine therapy reduced the increased expression of the regulator of G protein signaling 2 (RGS2) and restored the expression of collagen type I in the sclera of FDM animals (58). In atropine-treated scleral fibroblasts, Hsiao *et al.* (136) applied bioinformatics and next-generation sequencing techniques to identify genes with different expressions, as well as microRNAs. They discovered that scleral remodeling may be reduced by mechanisms that blocked melatonin breakdown during the night. The associations between miR-2682-5p-PRLR and miR-2682-5p-KNCJ5 in scleral fibroblasts offered a scientific basis for evaluating the contribution of low-dose atropine therapy (136).

Zou *et al.* (70) in their paper demonstrated that treatment with atropine lessened the effects of FDM on alterations in refraction, axial length, and scleral remodeling. Intriguingly, atropine administration markedly lowered RGS2 mRNA and protein expression in the sclera of the FDM eyes while vastly increasing collagen type I mRNA expression (70). Barathi and Beuerman also reported reduced progression of myopia in atropine treated mice (69). According to their study, 1% atropine slows the progression of myopia in mouse eyes from both pigmented and non-pigmented mice. With atropine administration, both eyes, with pigmentation and those without, changed refractive state from myopic to a physiological range of minimal or no refractive error. Atropine therapy had no statistically significant effect on corneal thickness, anterior chamber depth, corneal curvature, or retinal thickness. After taking atropine, the lens thickness and vitreous chamber depth were decreased substantially. In myopic sclera following atropine administration, real-time PCR revealed that mRNA levels for muscarinic receptors M1, M3, and M4 were increased, while M2 and M5 exhibited no change (69).

In another paper, researchers examined the effect of 1% atropine on progression of myopia in contact lens wearing guinea pigs (137). By the sixth week, there were statistically significant differences between the atropine-treated and control groups (for spherical equivalent refractive error and axial length). The treated eyes of the control group had greater axial elongation and advancement of myopia compared to both the daily atropine and every three-day atropine groups. The area of choroidal blood vessels reduced with time in the treated eyes of the control group, along with overall choroidal thinning; these effects were mitigated by atropine. While retinal thickness decreased during the course of the treatment, atropine had no effect on it (130). Scleral thickness was reduced at the equatorial and posterior regions as a result of spectacle lens-induced myopia paired with daily injections of normal saline. Myopia caused by lenses was prevented from progressing by daily injections of atropine sulphate at a dosage of 1% (69). Atropine injected intravitreally into the retina of chicks resulted in a rise in both the release of dopamine and the levels of its metabolite DOPAC (131) and decreased the elevated GABA transporter-1 (GAT-1) and, to a lesser amount, GAT-3 protein levels that were present in the mouse retina after LIM treatment (132). Beyond atropine, selective muscarinic antagonists such as pirenzepine and himbacine have been investigated for their potential to inhibit experimental myopia. Pirenzepine is a selective M1 and M4 muscarinic receptor antagonist in mammals and primarily affects M2 and M4 subtypes in chicks (73, 140, 141). Its antimyopic efficacy has been demonstrated in multiple animal models, including chicks and tree shrews. In chicks, pirenzepine

significantly suppressed form-deprivation myopia in a dose-dependent manner (73). In tree shrews, pirenzepine was shown to reduce ocular elongation and prevent myopic shifts induced by lens wear, suggesting its effectiveness is conserved across species with a well-developed accommodative system (140). Importantly, pirenzepine has also been evaluated in human clinical trials. A randomized, double-masked, placebo-controlled study involving 174 children aged 8 to 12 years demonstrated that 2% pirenzepine ophthalmic gel significantly slowed myopia progression over a one-year treatment period (142).

Himbacine, another muscarinic antagonist with preferential activity at M2 and M4 receptors, has also been tested in the chick model, demonstrated that himbacine effectively inhibited form-deprivation-induced axial elongation (143). Importantly, their findings implicated the M4 receptor as a likely mediator of the antimyopic effects, given the pharmacological profile of himbacine. These results provide support for the hypothesis that muscarinic signaling, particularly *via* the M4 receptor subtype, is involved in scleral remodeling and axial growth regulation (143).

CONCLUSIONS AND PROPOSED FUTURE WORK

Decades of research using experimental models have fundamentally advanced our understanding of myopia development, establishing that visually guided mechanisms actively modulate postnatal eye growth. Key findings reveal that the neuroretina locally detects and processes optical defocus signals, including both the presence and changes in defocus, initiating a signaling cascade that extends through the RPE and choroid to modulate scleral extracellular matrix remodeling and, consequently, axial length. This process involves dynamic changes in choroidal thickness and is influenced by a host of molecular mediators. Notably, retinal dopamine has been identified as a crucial inhibitory signal against excessive eye growth, with acetylcholine and retinoic acid also playing significant roles. Furthermore, investigations into genetic predispositions and a spectrum of -omics studies are increasingly elucidating the complex gene networks, diverse signaling pathways (such as those involving light processing, circadian rhythms, and metabolic functions), and potential biomarkers that contribute to the multifactorial nature of myopia.

While very significant advances have been made over the past few decades in the understanding of the mechanism of myopia development, there remains some important details that need to be explored. For example, future research should focus on further unraveling retinal signal processing, from identifying the specific signals within layers like the inner plexiform layer that detect temporal changes in blur, to understanding how these signals are subsequently integrated and stored to modulate axial growth rates. This investigation into growth control also needs to clarify the interplay between pre-programmed directives potentially residing locally within retinal and scleral cells versus those guided by higher neural centers. In parallel, the pervasive influence of nearwork requires a deeper dive into its neurobiological impact, including the acute retinal neurochemical changes during transient myopia, and critically, how the cumulative effects of such repeated visual tasks are processed within retinal networks over time to ultimately contribute to scleral matrix weakening and the progressive axial elongation characteristic of myopia development. Addressing these interconnected challenges in visual information processing and ocular growth regulation will be pivotal for advancing our ability to manage the progression of myopia.

Future work on myopia could also draw from broader research into other ocular and systemic diseases that affect the retina. For example, studies have highlighted the potential of non-invasive monitoring by identifying systemic biomarkers of autophagy in AMD (144) and by tracking structural retinal changes, such as ganglion cell layer thinning, after severe COVID-19 infection (145). In parallel, research into novel therapeutic approaches has demonstrated the anti-inflammatory potential of natural compounds targeting key retinal signaling pathways (146). Exploring whether similar systemic markers, imaging-based structural changes, or novel therapeutic strategies are relevant to progressive myopia could offer new avenues for understanding its pathomechanism and management.

Conflict of interest statement: Bartosz Machna and Maciej Oseka are employees of Oftalabs; Adrian Smedowski and Anna Pacwa are employees of GlaucoTech.

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Received: March 11, 2025
Accepted: August 31, 2025

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