DOPAMINE, THE CHOROID, AND EMMETROPIZATION

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Balprit Dhillon

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This manuscript has been read and accepted by the
Thesis Committee in satisfaction of the
thesis requirement for the degree of Master of Science

Signed by:
Debora Nickla
A56E4EE32023408...

______________ Date

Debora L. Nickla, Ph.D.
Graduate Faculty Advisor

DocuSigned by:
78A8AD972399447...

Thanasis Panorgias, Ph.D.
Thesis Committee Member

DocuSigned by:
Sangeetha Metlapally
EE5BE7B95D304CA...

Sangeetha Metlapally, Ph.D
Thesis Committee Member

DocuSigned by:
AF550B737FF84DA...

Xiaoying Zhu, Ph.D., OD
Thesis Committee Member

DocuSigned by:
78A8AD972399447...

______________ Date

Thanasis Panorgias, Ph.D.
Director of Graduate Studies

Abstract

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Balprit Dhillon

New England College of Optometry, 2025

The rise in levels of global myopia has led to increased research to further understand the mechanism behind this refractive state. Experiments in animal models have helped create management options for myopia control. Early experiments began with lid suture and diffusers, and spectacle lenses were later developed to allow for myopic and hyperopic defocus. These vision altering devices allowed for manipulations of the visual environment to help understand the anatomical control mechanisms regulating the parts of the eye. Through these manipulations, changes in choroidal thickness and axial length were observed in several different animal models. Studies involving optic nerve section led to the hypothesis of local ocular growth regulation, implying signal communication between the retina and sclera. To attain further understanding of the signal cascade, agonists and antagonists of potential neurotransmitters were used in the eyes. Dopamine has been highlighted as a potential molecule involved in vision regulation given its numerous roles within the eye. From results of experiments with agonists and antagonists, retinal D2-like receptors have been shown to be involved in the choroidal thickening and ocular inhibition response. In form deprivation myopia, dopamine likely acts to prevent axial elongation. Further research will help determine the role of dopamine as a treatment option for myopia.

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I would like to thank Dr. Debora Nickla for her unwavering support and insight.

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And lastly, thank you Mandeep for all that you do.

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Chapter 1: Introduction to Myopia

Myopia has become a global epidemic. According to current data on myopia prevalence and global population numbers, rates of myopia are expected to increase to 52% by 2050. In 2010, that rate was at 27% (Nouraeinejad, 2017; Nouraeinejad, 2020; Holden et al.,2016); therefore, a predicted increase of 25% over a 40-year period. Currently, the sixth leading cause of blindness is complications from axial elongation in myopia (Cooper and Tkatchenko, 2018).

Myopia is defined as a refractive error resulting from light from a distant object focusing in front of the retina caused by increased curvature of the cornea or excessive axial elongation. Several theories have been proposed to explain the development of myopia. Genetics may play a role as research has shown that parents who were both myopic had offspring that were 6.42 times as likely to be myopic, when compared to children with parents without myopia or one parent with myopia (Pacella et al., 1999). Genome-wide association studies revealed genetic loci linked to refractive error (Soluki et al., 2010). Near work and reading have also been observed to be a factor in myopia progression (Hepsen and Evereklioglu and Bayramlar, 2001). There is increased presence of myopia in those with advanced education and decreased outdoor time (Lee et al., 2013; Zadnik and Mutti, 1987). Some studies have suggested that a lag of accommodation in myopic children may be the cause of continued progression (Gwiazda et al., 1993) (Gwiazda et al., 2005).

Myopia can start at any age. In 2025, Pan and group assessed rates of myopia in children in China. They concluded that the overall myopia prevalence was 36.6%. Age based results were 2.6% in ages 0-4, 22.0% in ages 5-9, 45.4% in ages 10-14, and 67.2% in ages 15-19.

As myopia continues to increase to over a power of -6.00, detrimental changes can occur. High myopia can result in choroidal neovascularization, retinal detachment, cataract, glaucoma and myopic macular degeneration. These conditions can result in visual impairment and blindness. In Japan, 12.2% of vision impairment was a result of myopic macular degeneration (Yamada and Hiratsuka and Roberts, 2010). If in fact, the future predictions by Holden and group end up to be true, then the greatest numbers of global cases of permanent blindness would be from consequences of myopia (Holden et al., 2016).

Myopia Control

There is a global response to the alarming prevalence of myopia. There is emerging research, novel treatments and new tools for management. Current treatment options for myopia control include contact lenses, single vision, progressive or bifocal spectacle lenses, atropine and orthokeratology.

The first FDA approved myopia control contact lens developed for children was the MiSight lens by Coopervision Inc. This daily disposable contact lens features a concentric design with a central ve error, which is considered the correction zone. The next outer concentric ring of power is the +2 diopter treatment zone. The lens has alternating rings of correction and treatment zones and the treatment zones lead to myopic defocus (Ruiz-Pomeda et al., 2018). See Figure 1. Clinical trials have shown that the lens reduces axial elongation and myopia progression (Ruiz-Pomeda et al., 2018).

Figure 1. Design of MiSight Contact Lens

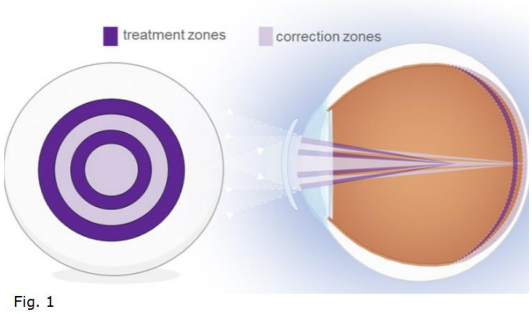

Fig. 1
Source
A 3-year Randomized Clinical Trial of MiSight Lenses for Myopia Control. Optometry and Vision Science96(8):556-567, August 2019.

Spectacle lenses have been

Miyosmart spectacle lens was created for myopia control. The lens has a central distance correction zone with an outer area containing small lenslets, each made of an increased +3.5 diopter of power. This design is considered as Defocus Incorporated Multiple Segments (DIMS). Research studies have shown significant decrease in myopia progression and axial length with DIMS lenses when compared to single vision lenses (Lam et al., 2019). Progressive and bifocal lenses were used more frequently in the past. However, studies did not yield a major difference in myopia progression between progressive and single vision lenses (Edwards et al., 2002). Executive bifocal, on the other hand, was observed to decrease both myopia progression and axial length (Cheng et al., 2014).

Many years ago, clinicians discovered the effect of atropine on myopia control. In a 1989 study, 1% atropine was observed to slow down myopia progression in children (Yen et al., 1989). Atropine sulfate causes paralysis of the ciliary muscle and leads to cycloplegia. It is used regularly in some countries for cycloplegic refractions. Many international clinical trials in children using low dose atropine, have resulted in the slowing down of myopia (Heida et

al, 2021; Saxena et al., 2024). Atropine at concentrations of less than 1%, has become a commonly prescribed eye drop in the control of myopia.

Orthokeratology is a process where a rigid gas permeable contact lens is worn overnight to flatten the cornea, leading to a decrease in myopic power. Although it was initially used to cause a temporary change in the power of the eye, such that no correction would be needed during the day, it was discovered that it also slowed down myopia progression (Cho and Cheung and Edwards, 2005).

There has been much interest in myopia research which correlates with a greater number of scientific research articles. In 2022, Shan and group accessed 11,172 articles on myopia studies published between 1900 and 2020 from the Web of Science database. They found that not much had been published before 1990. But after 1991, there was a significant increase from 100 to over 400 after 2011. In 2020, there were 822 publications (Shan et al., 2020).

Chapter 2- Myopia Research with Animal Models

In the last 30 years, there has been a significant increase in myopia research. Much of this research would not have been possible without the use of animal models nor without innovative experimental designs. These studies have led to new discoveries in many areas of vision science and have propelled the development of new treatment modalities.

Form Deprivation Myopia

In 1975, Wiesel and Raviola performed experiments on the eyes of macaque monkeys. They surgically fused the eyelids for one year and observed axial myopia. The animals were maintained in a 12 hour light and 12 hour dark schedule (Wiesel and Raviola, 1979). This technique laid the foundation for future experimental myopia research. The development of myopia in this type of experimental design was labelled as deprivation myopia or form deprivation myopia, implying that the retinal stimuli was unclear as it was of low contrast and spatial low-pass filtering (Bartmann and Schaeffel, 1979). Lid suturing however, also led to other changes within the eye. The cornea was flatter, both the anterior and vitreous chamber had increased depth and there was increased axial and equatorial growth (Kang et al, 2024; Gottlieb et al., 1987). The temperature also decreased in lid sutured chick eyes (Hodos and Kuenzel, 1993). Lid suturing has been performed in tree shrew, chicks, cats, rhesus monkey, piglets, C57BL/6J mice, guinea pigs, rabbits and golden Syrian hamster (Sherman and Norton and Casagrande, 1997; Yinon et al, 1983; Kirby and Sutton and Weiss, 1982; Green and Guyton, 1986; Shih et al., 1998; Tejedor and De la Villa, 2003; Lu et al, 2006; Gao et al., 2006; Lin et al., 2021). Diffusers were also used to achieve form deprivation myopia as they did not cause corneal flattening, require sutures or decrease

ocular temperature. Diffusers were used in Guinea pigs, C57BL/6J mice, rabbits, tree shrews, marmoset, chicks, Syrian hamsters, rhesus monkeys (Bowrey et al., 2015; Tkatchenko and Shen and Tkatchenko, 2009; Kim and Hwang and Yang, 2025; She and Gawne and Ward, 2023;Troilo and Nickla, 2005; Wallman and al., 1995; Lin et al., 2021; Huang et al., 2009). In 2020, Zi et al. observed that after lid suturing the eyes of guinea pigs, there were fewer ganglion cell and inner and outer nuclear layers. The overall organization of the layers had altered and both the retina and sclera were thinner. Form deprivation myopia was not an ideal way to understand the mechanism of ocular growth as there were no visual cues. It was considered to be an open loop feedback system as the eye could not make adjustments to enhance the clarity of the retinal image. The eye simply continued to grow without any control mechanism.

Lens-Induced Myopia and Hyperopia

Researchers began using lenses of both positive and negative power on different animal models. This was a fundamental shift in the experimental approach to myopia research. With lenses, it is not a complete open loop system since the image blur decreases during eye growth (Schaeffel and Swiatczak, 2024). This would help further the understanding of the emmetropization process of the human eye which operates as a closed loop system. In a closed loop system, the eye will make modifications to increase the quality of the retinal image. Through these experiments with transparent negative and positive powered lenses, the animals could make adjustments to improve retinal image clarity. In 1988, Schaeffel fitted chickens with negative and positive lens powers and made several assessments including axial length and refraction. They found that the positive lenses led to hyperopic

refractions, while the negative lenses resulted in myopic refractions (Schaeffel and Glasser and Howland, 1988). A negative lens refracts the light past the plane of the retina. To allow clarity of vision, the eye must elongate for the retina to meet the converging rays. Therefore, a minus lens caused hyperopic defocus and a myopic refraction resulted after the lens was removed due to the increase in axial length. A positive lens converges rays in front of the retina, as does myopia. To allow image clarity, the retinal plane will shift anteriorly. This was observed by a decrease in vitreous chamber depth and a shorter axial length (Zhu et al., 2013). A positive lens resulted in myopic defocus and after lens removal, a hyperopic refraction. Accommodation is likely not involved in these responses with lenses, as they persisted despite lesions to the Edinger-Westphal nucleus in chick eyes (Schaeffel et al., 1990). Lens experiments have been performed in the following animal models: kittens, chicks, rhesus monkeys, tree shrews, marmosets, guinea pigs and C57BL/6J mice (Smith and Watson and Maguire, 1980; Schaeffel et al, 1980; Zhu et al., 2013; Cottrial and McBrien, 1996; Graham and Judge, 1999; Howlett and McFadden, 2009; Tanaka et al., 2019). In experiments using diffusers or negative lenses, it was found that daily periods of vision without the diffusers or lenses, prevented form deprivation myopia (FDM) and lens induced myopia (LIM) (Napper et al., 1995; Nickla, 2007).

Local versus Regional Control

Researchers performed experiments on chicks with optic nerve section. Eyes with optic nerve section became highly hyperopic and smaller. This is in contrast to normal eyes which grow to achieve emmetropia. Another set of eyes with optic nerve section had translucent occluders cover either the nasal or temporal retina. In both sets, significant amounts of

myopia resulted in the same occluded region. This revealed that despite disconnecting the nerve from the brain, myopic changes were still observed in the retina of these eyes. This led researchers to hypothesize that local ocular growth regulation could be controlled by the eye itself, that is, through communication between the retina and sclera. However, given the expected emmetropization of the normal eye, the impact and influence of the brain in regulating ocular growth would also need to be considered (Troilo and Gottlieb and Wallman, 1987). Hyperopic defocus in chick eyes with optic nerve section did not display changes in scleral growth or choroidal thinning that would otherwise be expected in non-sectioned eyes (Wildsoet and Wallman, 1995). Therefore, eyes with optic nerve sections likely process FDM and LIM in separate ways. Further experiments determined regional control within the eye. Experiments designed for form deprivation in the nasal and temporal retina in chicks, led to myopia in the nasal and temporal retinas, respectively. This revealed that select regions of the retina could change without impacting other regions, and that these individual regions could impact growth of the eye in the corresponding area (Wallman et al., 1987). The peripheral retina was considered to regulate ocular growth as axial length changes persisted with a diffuser lens in monkeys with macular ablation (Smith et al., 2007). Peripheral myopic defocus resulted in more hyperopic central refractive errors, demonstrating that altering the peripheral visual experience could affect the central power of the eye (Smith et al., 2013). Therefore, ocular growth regulation is not only controlled by the eye as a whole, but also by regional control factors within the eye.

Experiments on different animal models have shown similar results for form deprivation and hyperopic defocus alluding to a common growth regulation process.

Variations between Animal Models

Common animal models include: monkeys, tree shrews, guinea pigs, mice and chicks. Although some models are more anatomically aligned with the human eye, differences do exist. The human eye consists of rods, three types of cones and a foveal structure. Monkeys anatomically have a fovea that is similar to the human eye. They also have a similar rod to cone ratio of 20:1(Bowmaker et al., 1978). The eyes of a tree shrew are mainly composed of cones, but it does not have a fovea nor a choriocapillaris in the choroid (Sajdak et al., 2019; Norton, 1999). Unlike the human eye, guinea pigs do not have a vascular network in the retina. Mice have retinal vasculature, but differ in overall size and in the size of the lens and vitreous cavity (Schmucker and Schaeffel, 2004). The chick eye is void of a fovea and instead has an area with a large density of cones (Kostic and Arsenijevic, 2016). It also has six types of photoreceptors and the cone to rod ratio is 3:2. The retina of a chick eye also does not contain a vascular network. Instead, within the vitreous lies the pecten. The pecten is joined to the choroid and is made of vascular and glial tissue (Nava et al., 2016). Experimental myopia studies observed varying changes in the sclera between chick and human eyes. The ciliary muscle fibers in chick eyes are striated whereas in human eyes they are smooth. Muscarinic receptors are predominant in human eyes, and chick eyes have both nicotinic and muscarinic acetylcholine receptors (Pilar et al., 1987). The sclera of the chick eye contains Type II collagen in the cartilage and fibers. In humans, the sclera is made of several collagen types and proteoglycans. It consists of predominately Type I with minor amounts of III and V (Rada et al., 1992). Changes were noted in proteoglycan synthesis in the sclera of chickens during form deprivation. The rate of proteoglycan synthesis in chick

eyes increased during form deprivation and then decreased after the occluder was removed (Rada et al, 1992). Human eyes with high myopia have been noted to have a thinner sclera with less collagen (Dong et al., 2019). It has been observed that most neonates in a number of species are generally hyperopic and then gradually shifts to emmetropia. Animal models have been useful in myopia research due to the high reproducibility rate, rapid development, and fast compensation to FDM and lens defocus (Troilo et al., 2019).

Role of the Choroid

The choroid was implicated in the ocular growth response as it was observed that its thickness changed in response to diffusers and lenses. Form deprivation myopia in chicks led to an increase in vitreous chamber depth and a thinner choroid. However, during recovery, the choroid had thickened. It was thought that the change during recovery was an attempt to move the retinal plane more anterior and thus improve image quality. When positive lenses were used, the myopic defocus led to choroidal thickening. When the lenses were removed, the eyes were hyperopic and the choroidal thickness subsequently decreased. Negative lenses created hyperopic defocus and the choroid decreased in thickness. When the lenses were removed, the eyes were now myopic, and a shift resulted with the choroid thickening over time (Wallman et al., 1995). Eyelid suture in chicks also led to changes in the choriocapillaris and caused a decrease in density, capillary diameter, endothelial fenestrations (Hirata and Negi, 1998).

Conclusion

Animal studies have had a profound impact on the understanding of ocular growth and development of myopia. The discovery of changes in ocular anatomy as a result of FDM and spectacle lens shed new light on the ability of the eyes to make such modifications.

The impact of peripheral visual experience on the central power of the eye has led to further research. More studies began focusing on the choroid after it was noted to change in FDM and lens defocus experiments. Ultimately, this led to further clinical trials in humans leading to the development of new myopia control options.

Chapter 3: The Choroid

The choroid is a vascular tissue located between the retina and sclera. Anteriorly, it forms the ciliary body. It was initially thought that the function of the choroid was to supply blood to the outer retina. However, research with ultrasonography, electron microscopy and optical coherence tomography has allowed for further analysis of structure and function.

Choroidal Anatomy and Function

layer and the suprachoroidal layer. The human choroid is estimated to be 200 μm at birth and the thickness decreases with age. At age 90, it measured 80 μm (Ramrattan et al., 1994). The choroid contains blood vessels, fibroblasts, resident immunocompetent cells, non-vascular smooth muscle, intrinsic choroidal neurons, melanocytes, collagenous and elastic connective tissue (Nickla and Wallman 2010).

RPE, inner collagenous layer, elastin layer, outer collagenous layer and basal lamina of the choriocapillaris (Hogan, 1961)

maintaining space between the retina and choroid. It controls the flow of molecules between these two parts and prevents cellular migration (Booij et al., 2010; Jonas et al., 2017; Murali et al., 2020).

The choriocapillaris contains capillaries with fenestrations in portions facing the retina. The size and density of the capillaries changes with location as they are smaller and more closely

arranged near the macula. They are larger and further spaced apart as they approach the equatorial region (Olver, 1990). The thickness at the fovea is 10 μm (Nickla and Wallman, 2010). Choriocapillaris serves as a two-way transporter by supplying water, oxygen, micronutrients and ions to the outer retina and it delivers photoreceptor waste to the capillary bloodstream (Borrelli et al., 2019; Wangsa-Wirawan and Linsenmeier, 2003; Yu et al., 2014). The capillaries maintain choroidal blood flow (Olver, 1990).

choriocapillaris, respectively.

131 μm below the fovea (Zhao et al., 2018) of arteries and veins and its thickness ranges between 89 to 221 μm below the fovea. The stroma within these layers includes the following: fibroblasts, non-vascular smooth muscle cells, collagen and elastic fibers, macrophages, mast cells, lymphocytes and melanocytes (Nickla and Wallman, 2010). These layers also contain lacunae, however, their function in humans is unknown.

and collagen fibers. It serves as a boundary between the choroid and the sclera (Nickla and Wallman, 2010).

The choroid assists in the regulation of ocular growth, thermoregulation of the retina, and maintains blood flow to the outer retina. It produces growth factors and it provides a route for aqueous humor drainage from the anterior chamber.

Choroid and Animal Anatomy

There are several differences between the choroid of humans and animals. Firstly, the thickness varies. In chickens, the thickness is around 250 μm and in non-humans primates, its 95 μm at the fovea (Krebs and Krebs, 1991; Wallman et al., 1998; Nickla and Wildsoet and Wallman, 1998). The choroidal lacunae in chick eyes are part of the lymphatic system (De Stefano and Mugnaini, 1997). It has been shown that the volume of the lacunae can shift significantly and contribute to the change in choroidal thickness (Junghans et al., 1999). The number of melanocytes has been shown to vary between animals (Krebs and Krebs, 1991; De Stefano and Mugnaini, 1997).

Choroidal Innervation

Control of choroidal blood flow is managed by several neural networks. These networks innervate the smooth muscle of blood vessels, and the stromal non-vascular smooth muscle and intrinsic choroidal neurons. The parasympathetic system has cholinergic fibers that release the vasodilators vasoactive intestinal polypeptide (VIP) and nitric oxide (NO). In humans, the parasympathetic innervation is from the pterygopalatine ganglion, but in birds, it comes from both the ciliary ganglion and the pterygopalatine ganglia (Ruskell, 1971). The ciliary fibers release acetylcholine, somatostatin and nitric oxide. For the sympathetic pathway, input originates from the superior cervical ganglion for both birds and humans (Klooster et al., 1996; Nickla and Wallman, 2010). It is carried by noradrenergic fibers and release noradrenaline which causes vasoconstriction. Sensory innervation exists through peptides such as substance-P and calcitonin gene-related peptide which cause vasodilation

(de Hoz et al., 2008). Intrinsic choroidal neurons were discovered in humans, tree shrews and birds (Flugel et al., 1994; Flugel-Koch and Kaufman and Lutjen-Drecoll, 1994; Bergua and Mayer and Neuhuber, 1996). Although their role is not fully understood, they have been found to innervate vascular and non-vascular tissue (Schrodl et al., 2003). Non-vascular smooth muscle is most likely innervated by both the parasympathetic and sympathetic system (Nickla and Wallman, 2010).

Choroidal Changes in Myopic Eyes

Myopia has been shown to affect the choriocapillaris through increased intercapillary distances and decreased choroidal blood flow (Al-Sheik et al., 2017; Akyol et al., 1996). High myopia can lead to chorioretinal atrophy causing loss of the RPE and choriocapillaris (Sayanagi et al., 2017). Choroidal neovascularization is a serious complication of high human myopic eyes (Alshareef et al., 2017).

Choroid and Animal Myopia Studies

The 1995 landmark study showed that the choroidal thickness of chicks changed in response to diffusers and lenses (Wallman et al., 1995). Changes in the choroid have been observed in chickens, macaques, guinea pigs and marmosets (Howlett and McFadden, 2009; Troilo and Nickla and Wildsoet, 2000; Hung and Wallman and Smith, 2000). The choroid can compensate for defocus ranging from -15 D to +15 D (Wildsoet and Wallman, 1995). In the chick eye, increased choroidal thickness is accompanied by an increase in the size of the lacunae (Wallman et al., 1995). An increase in choroidal proteoglycan synthesis and

choroidal thickness was also noted in chick choroids that wore +15 D spectacle lens. Further studies showed that ocular diurnal rhythms are associated with eye growth, with choroids of chicken eyes thickening around 100 microns per day, with the greatest thickness observed at night (Nickla, Wildsoet and Wallman, 1998).

Thinning of the chick choroid in form deprivation myopia (FDM) ceases during brief exposure to normal vision and stroboscopic illumination as choroidal thickening was present (Nickla, 2007). During the first three days of recovery from FDM in chicks, a significant increase in Na^+ and Cl^- ions was observed and this correlated with an increase in choroidal thickness and edema (Liang et al, 2004).

The choroidal response in myopia studies is thought to be part of a triad of reactions working together to improve retinal image quality. It is considered to be a change that is slower than accommodation, yet faster than scleral extracellular matrix synthesis (Troilo et al., 2019).

Theories to Explain Changes in Choroidal Thickness

Several theories were hypothesized to explain the changes in choroidal thickness. There are increased levels of choroidal proteoglycan synthesis during recovery from FDM. The proteoglycans absorb water and this could lead to increased thickness, however there is not a significant amount of synthesis (Nickla and Wallman, 2010). Fluid consisting of ions and water from the retina and RPE to the choroid could increase thickness through edema (Rymer and Wildsoet, 2005). The capillaries may also play a role. Increase in permeability could allow an influx of protein into the ECM. Another pathway of influx to the choroid may be from the anterior chamber. The choroid, ciliary body and iris together form the uvea,

therefore it is possible for fluid from the anterior chamber to travel through these structures to the choroid. Studies have shown that enzymes injected in the anterior chamber were found in the suprachoroid hours later (Wallman et al, 1995).

Non-vascular smooth muscle in the choroid could also account for the quick choroidal thickness changes by functioning as a muscular mechanism. (Nickla and Wallman, 2010). Therefore, either changes in fluids or impact from smooth muscle are the likely contributing factors affecting choroidal thickness.

Signal Cascade

Researchers have been trying to develop a signal cascade to help explain the order and action of potential molecules responsible for ocular changes in FDM and lens defocus. It is thought that messengers must be initiated at the level of the retina and pass through the choroid to elicit changes in the sclera. The retina is considered as the first step as it was shown that positive and negative lenses generate opposing responses from retinal neurons (Fischer et al., 1999). Input from the retina or RPE could direct the choroid to release growth factors that would control the scleral response. The choroid produces growth factors such as vascular endothelial growth factor (VEGF). When sclera was co-cultured with choroid from recovering eyes, it had lower glycosaminoglycans (GAG) synthesis. The opposite was true for FDM eyes (Rada et al., 1992). The choroid likely produces retinoic acid (RA) as it was shown that myopic defocus and recovery led to increased levels of RA in the choroid. GAG levels were decreased when retinoic acid was added to scleral tissue culture (Mertz and

Wallman, 2000). Therefore, production of retinoic acid within the choroid may influence the changes in the sclera.

Conclusion

The ability of the choroid to alters its thickness in response to visual manipulations led to further research into choroidal anatomy, function and mechanism of action. However, questions still remain. Analysis of several structures, including lacunae in the human choroid, intrinsic choroidal neurons and non-vascular smooth muscle, is necessary to fully understand the impact of the choroid in ocular elongation. Further research into the biochemistry of molecules within the choroid will help deduce it role in the signal cascade.

Chapter 4-Pharmacology of Myopia

Studies have examined the impact of signaling molecules on ocular elongation and choroidal thickness. For further analysis of a particular molecule, agonists or antagonists of that molecule were used to deduce its impact. These types of experiments have generated enormous data, helping researchers achieve greater understanding of the components involved in ocular growth regulation.

Nitric Oxide

Nitric oxide (NO) is a neurotransmitter and vasodilator. It is produced in several parts of the eye and mediates various functions including blood flow, neurotransmission and intraocular pressure (IOP), thus directly impacting the choroid, retina and optic nerve (Becquet and Courtois and Goureau, 1997). It is produced by the enzyme nitric oxide synthase (NOS) and interacts with guanylyl cyclase to produce cyclic guanosine monophosphate (cGMP). This leads to the activation of protein kinase G and MAP kinases and causes vasodilation (Duran and Beuve and Sanchez, 2013). There are three isoforms of NOS: neuronal form (nNOS), endothelial form (eNOS) and the inducible form (iNOS) (Nickla and Wallman, 2010). The endothelial form is mainly released from endothelial cells and affects vascular tone and microvascular hyperpermeability (Duran and Beuve and Sanchez, 2013). It also impacts IOP by increasing aqueous humor outflow through increased endothelial permeability of

(Reina-Torres, 2021). The inducible form is expressed as needed, primarily during infection and inflammation as a form of protection (Lechner and Lirk and Reider, 2005). The neuronal form is involved in

numerous physiological functions including synaptic plasticity, regulation of central blood pressure and smooth muscle relaxation (Fostermann and Sessa, 2012).

NO is found in many locations including intrinsic choroidal neurons, RPE, retinal neurons, axons terminals of ciliary and pterygopalantine ganglia and in the choroid (Flugel et al., 1994; Goldstein and Ostwald and Roth, 1996; Fischer and Stell, 1999; Sun and May, 1994; Yamamoto et al., 1993).

Chick eyes that had FDM and were given L-NAME (non-specific NOS inhibitor) injections before 2 hours of diffuser removal, did not obtain the myopia suppression normally observed with normal vision (Nickla et al., 2006). When N -propyl-L-arginine (nNOS inhibitor) and L-NMMA (non-specific NOS inhibitor) were injected in chick eyes, they prevented the expected choroidal thickening from myopic defocus and post diffuser removal in FDM eyes. N -propyl-L-arginine did not effect the anterior chamber and blocked the expected inhibition of scleral glycosaminoglycan synthesis for myopic defocus (Nickla and Damyanova and Lytle, 2009). L-NAME led to choroidal thinning in both normal, recovering and positive lens wearing eyes (Nickla and Wildsoet, 2004). In experiments without drug treatments, it has been shown that in recovering eyes and positive lens wearing eyes, the vitreous chamber and anterior chamber depth decreases (Zhu et al., 2013). L-NAME prevented this decrease in vitreous chamber depth (Nickla and Damyanova and Lytle, 2009).

Dopamine has been linked to nitric oxide production (Fujiyama and Masuko, 1996). Flickering lights have also been shown to stimulate NO production from the retina (Neal and Cunningham and Matthews, 1998). Nitric oxide is suspected to impact the non-vascular

smooth muscle within the choroid as it is a smooth muscle relaxant and NAPDH (cofactor for NO production) was found to be located proximally to smooth muscle in the choroid (Bredt and Snyder, 1992; Poukens and Glasgow and Demer, 1998; Nickla and Damyanova and Lytle, 2009). The increase in scleral GAG by an inhibitor of nNOS may imply an effect of NO on the sclera (Nickla and Damyanova and Lytle, 2009). It is likely that NO acts on the choroid and is involved in growth inhibition and regulation of choroidal thickening during myopic defocus.

Acetylcholine

The eye contains muscarinic acetylcholine receptors that respond to the neurotransmitter acetylcholine and support the parasympathetic system. There are 5 receptor subtypes (M1-M5). There has been research using various drugs including atropine (non-selective antagonist), pirenzipine (M1 and M4 antagonist), oxyphenonium (non-selective antagonist) and scopolamine (M1 antagonist). Within the eye, muscarinic receptors are located in several parts including the cornea, iris, retina and sclera (Liu et al., 2007; Li et at., 2007; Mitchelson, 2012).

Atropine has been used extensively in experiments in chicks, humans, tree shrews and monkeys (Schwahn and Kaymak and Schaeffel, 2000; Schmid and Wildsoet, 2004; Kennedy et al., 2000; Mckanna and Casagrande, 1981; Tigges et al., 1999). It has prevented myopia and form deprivation myopia. Atropine was shown to inhibit axial elongation of the anterior and posterior parts of the deprived chick eyes. In the past, researchers believed that atropine inhibited myopia by relaxing accommodation. However, that was later proven false as

intravitreal injections of atropine prevented FDM in chick eyes. Chick ciliary muscles contain mostly nicotinic receptors and it was shown that atropine does not affect pupillary constriction to light (McBrien and Moghaddam and Reeder, 1993). Also, atropine was able to prevent FDM in the grey squirrel, which is a non-accommodating mammal (Bill et al., 1976). A

changes within the sclera or indirectly through other retinal neurotransmitters.

Muscarinic agonists and antagonists have been shown to impact choroidal thickness. Muscarinic antagonists atropine, oxyphenonium and pirenzipine led the choroid to thicken, whereas agonists oxotremorine, carbachol and arecaidine produced choroidal thinning. In vitro studies using drugs tested in eyecups of RPE, choroid and sclera found that muscarinic agonists (oxotremorine, pilocarpine, carbachol and arecaidine) led to choroidal thinning as opposed to antagonist pirenzepine which caused choroidal thickening (Nickla and Zhu and Wallman, 2013). In human clinical trials, the LAMP study showed choroidal thickening with atropine use (Yam et al., 2022).

Researchers have tried to determine which receptors are involved in axial length regulation.

Studies using atropine showed that scleral M3 expression was impacted in Syrian

Hamsters (Lin et al., 2012). Other muscarinic antagonists that were selective for M1 and M4, inhibited form deprivation myopia in tree shrews (Arumugam and McBrien, 2012). In chick eyes, Pirenzipine (M1 and M4 antagonist) prevented myopia and since M1 are not found in these eyes, M4 is likely the site of action (McBrien et al., 2009). Muscarinic receptors are located in various locations throughout the chick eye (Fischer et al., 1998).

It is apparent that acetylcholine is involved in ocular regulation. Atropine has already become a first line treatment for myopia control in humans. Assessing the effect acetylcholine has on the choroid and sclera will help deduce its role in the processing of vision. Choroidal thinning results as a response to FDM and hyperopic defocus as well as acetylcholine agonists. Therefore, acetylcholine may play a role in supporting the pathways for FDM and hyperopic defocus.

Dopamine

Dopamine is a neurotransmitter and neuromodulator and is involved in a variety of functions. In the eye, it is produced by retinal amacrine and interplexiform cells (Frederick et al., 1982). There are 5 dopamine receptor subtypes located in the retina. These subtypes are divided into two signaling pathways: D1-like receptors (includes D1R and D5R) and D2-like receptors (includes D2R, D3R and D4R) (Beaulieu and Gainetdinov, 2011). Molecules known for receptor specificity were used to determine receptor activity. Dopamine receptors are found in photoreceptors, RPE, amacrine and horizontals cells (Schorderet and Nowak, 1990). There has been extensive research on dopamine antagonists and agonists in many animal models.

To test the impact of dopamine on eye growth, other dopamine related molecules were used to examine axial length and refraction changes. Assessment with subconjunctival injections of dopamine agonist, apomorpine and antagonist, haloperidol showed a decrease in axial elongation but not equatorial elongation. Both molecules are considered nonselective and prefer D2 dopamine receptors (Stone et al., 1989). Apomorphine inhibited FDM in monkeys, chickens, guinea pigs and mice (Iuvone et al., 1991; Rohrer and Spira and Stell, 1993; Dong

et al., 2011; Yan et al., 2015). Apomorphine prevented lens induced myopia in chicks (Nickla and Totonelly and Dhillon, 2010).

Table 1. Actions of dopamine agonists and antagonists on choroidal thickness in negative lens wearing chickens from Nickla D, Totonelly K, and Dhillon B (2010).

Drug	Drug	Receptor Details	Choroidal response 3 hours after injection
Agonist	Apomorphine	Non-Specific	Thickened
	Quinpirole	D2/D4 Selective	Thickened
	SKF-38393	D1 Selective	No effect
Antagonist			
	Methylergonovine	Non-Specific	No effect
	Spiperone	D2/D4 Selective	No effect
	SCH-23390	D1 Selective	No effect

Research studies examined the impact of dopamine drugs of different receptor specificities on choroidal thickness. Daily injections of dopamine agonists were given for 4 days in negative lens wearing chicks. The results varied depending on drug receptor affinity. Apomorphine (non-specific) and quinpirole (D2/D4) inhibited both axial elongation and the expected myopia, and led to transient choroidal thickening. The choroidal thickening was not sustained throughout the experiment as an overall thinning was noted. SKF-38393 (D1) did not impact axial elongation or choroidal thickening. See Figure 2.

Dopamine antagonists were also utilized to determine if they were able to impact ocular changes from 2 hours of daily vision, as daily vision has been shown to prevent myopia. Daily vision implies no lens was used. The drugs were injected in eyes prior to 2 hours of vision without lenses. Methylergonovine had no effect, but spiperone and SCH-23390

prevented the recovery process and eyes remained myopic. However, both were less myopic when compared to eyes with full-time lens wear, implying a partial refractive effect of these drugs. There was no effect on axial length and choroidal thickness by all the antagonists (Nickla and Totonelly and Dhillon, 2010). Other experiments have shown that spiperone caused choroidal thinning in untreated chick eyes (Mathis et al., 2022).

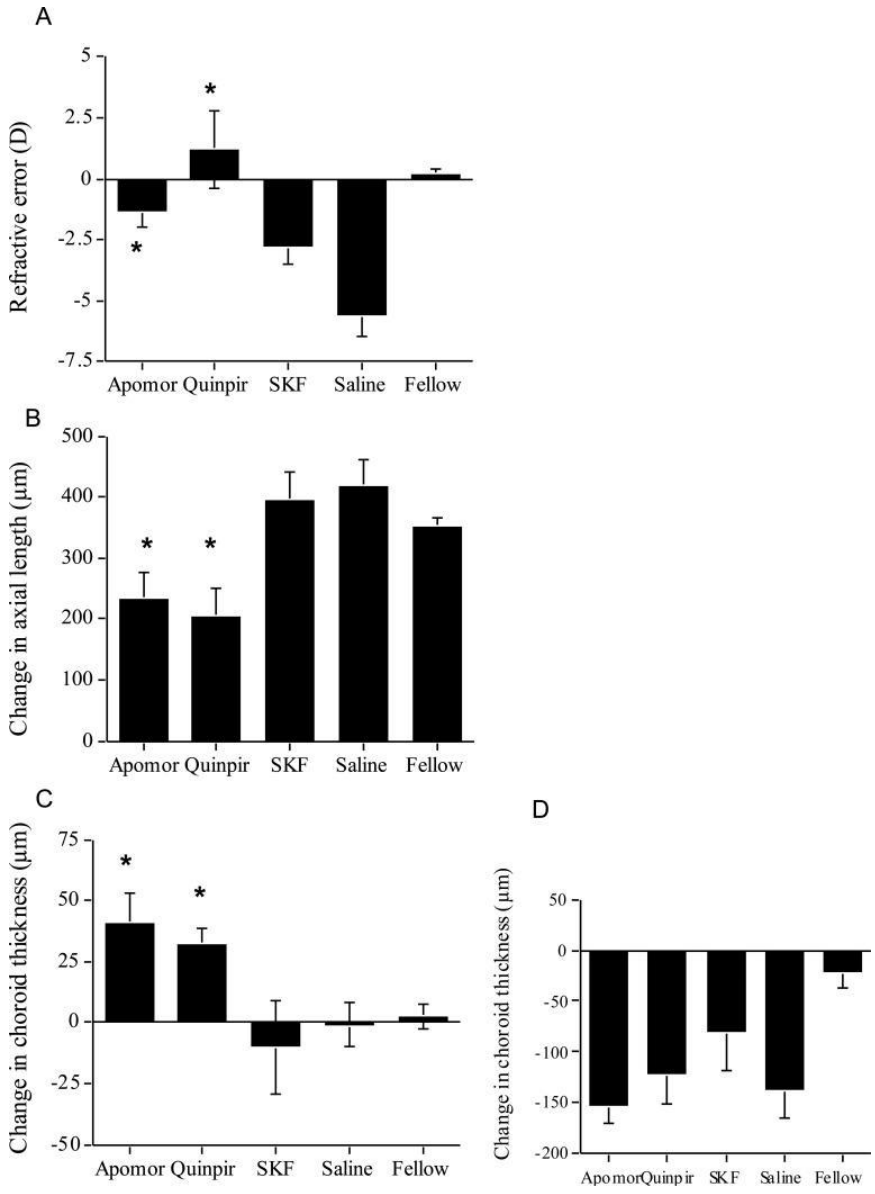

Figure 2. Results of experiment with three dopamine agonists A. Effect on refractive error B. Effect on axial length C. Effect on choroidal thickness. Part of this graph was reproduced with permission from: Nickla & Wallman, 2010 © Elsevier. D. Change in choroidal thickness over 4 days of the experiment.

(Nickla and Totonelly and Dhillon, 2010)

role as shown by 6-hydroxydopamine (6-OHDA), a neurotoxin that destroys dopamine neurons. It would have been expected that with less dopamine, increased axial elongation would occur, however, 6-OHDA inhibited FDM in chicks (Li et al., 1992; Diether and Schaeffel, 1997). 6-OHDA did not alter axial elongation when spectacle lenses were used, but it was later observed to reduce LIM with higher lens powers (Schaeffel et al., 1994). Also, variations in levels of dopamine can exist between each animal, and as a result, it was found that there was more resultant myopia in FDM in chicks with lower initial dopamine levels (Ohngemach and Hagel and Schaeffel, 1997). When dopamine precursor, Levodopa was administered through intraperitoneal injections in guinea pigs, dopamine levels rose and decreased deprivation myopia (Mao et al., 2010).

Experiments in chicks with diffusers or negative lenses that had intravitreal injections of both apomorphine and atropine, inhibited form deprivation myopia and lens induced myopia; however, a greater response was not generated with both drugs. Instead, Atropine alone was able to inhibit more myopia and prevent greater axial elongation (Schmid and Wildsoet, 2004).

Studies in monkeys utilizing topical 1% apomorphine HCL prevented form deprivation myopia (Iuvone et al. 1991). Dopamine may act as an intermediary in growth regulation as it causes the release of nitric oxide (Melis and Succu and Argiolas, 1996). In experiments with FDM and hyperopic defocus, dopamine was observed to play a role upstream to nitric oxide and choroidal changes, in the reaction mediating the inhibition of ocular growth (Nickla and Lee and Totonelly, 2013).

The function of dopamine based on results from experiments imply an important role for this molecule. Retinal D2-like receptors are likely involved in the choroidal thickening and ocular inhibition response. In FDM, dopamine probably acts to prevent axial elongation (Nickla and Wallman, 2010). A more extensive discussion on the role of dopamine will continue in the following chapter.

Conclusion

Through detailed analysis of nitric oxide, acetylcholine and dopamine, it is clear that these molecules are involved in the signaling cascade for changes in the choroid and axial length.

However, more research is needed to determine how dopamine and NO work together as well as their temporal relationship. Atropine is already used in children and 0.05% Atropine is preferred for myopia control (Yam et al., 2019). Further experiments could lead to new topical drugs to help prevent myopia progression and ocular health complications.

Chapter 5: The Role of Dopamine Within the Eye

Dopamine is involved in many functions in the human body including the central nervous system and peripheral organs (Channer et al., 2022). It is also found in the eye and plays a role in various processes.

Dopamine is involved in the processing of light.

Visual acuity is dependent on the retinal receptive field size. To optimize vision, the size changes according to illuminance (Feldkaemper and Schaeffel, 2013).

alternations in gap junctions between rods and cones (Zhou et al., 2017). When light levels are low, less dopamine is produced, and there is an increase in coupling of rod-cone gap junctions (Ribelayga and Cao and Mangel, 2008). The receptive field size becomes larger and this allows for vision in reduced lighting. In bright light, dopamine levels increases. As dopamine binds to D2 and D4 receptors, there is decreased adenylate cyclase, cyclic AMP and protein kinase A (Vaquero et al., 2001; Bu et al., 2014). Overall, there is less coupling of rod-cone gap junctions. As a result, receptive field sizes are smaller and acuity is sharper (Ribelayga and Cao and Mangel, 2008).

Gap junctions of horizontal cells and AII amacrine cells are controlled by the binding of the D1 receptor to dopamine. This results in the increase of adenylate cyclase, cyclic AMP and protein kinase A and reduces coupling . When the horizontal cell coupling decreases, the receptive field is smaller and this allows for an increase in contrast (Trenholm and Awatramani, 2019). For amacrine cell coupling, signals

are combined and photon noise removed (Smith and Vardi, 1995). Therefore, the release of dopamine regulates gap junctions of photoreceptors, AII amacrine and horizontal cells, and ultimately controls acuity and contrast in varying light levels.

Dopamine is involved in regulating circadian rhythms

Dopamine plays a role in the regulation of the circadian rhythm of the body and the eye. A circadian rhythm is controlled by the master clock, the suprachiasmatic nucleus, and will

- . Photoreceptors have endogenous clocks. A diurnal rhythm is led by the external light-dark cycle. In some species, retinal dopamine is circadian, while in others, it is diurnal. The natural circadian rhythm for dopamine results in elevated levels during the day and decreased levels at night (Dubocovich, 1983; Iuvone and Besharse, 1986). In form deprivation myopia experiments in chicks and monkeys, daytime levels of dopamine were exclusively found to be reduced but night levels were stable (Stone et al., 1989; Iuvone et al., 1989). Despite constant darkness, there is a circadian rhythm in levels of vitreal DOPAC, more notable during the light phase (Doyle and McIvor and Menaker, 2002).

Most eye growth has been noted to take place during the daytime in normal chick eyes. The chick eye was observed to grow during the day and shorten in the evening. During FDM, the eye grew during the day as well as at night. The axial elongation from FDM occurred because growth was not prevented at night (Weiss and Schaeffel, 1993). The amplitudes of the diurnal rhythm in FDM eyes were altered as a result of the excessive growth. In chicks, the axial length rhythm is circadian as a rhythm was present in darkness (Nickla and

Wildsoet and Troilo, 2001). Chickens under constant light of 120 lx did not have an axial length diurnal rhythm (Weiss and Schaeffel, 1993).

Dopamine is involved in the regulation of ocular growth

In 1989, researchers observed changes in retinal dopamine levels in chicks with form deprivation myopia (Stone et al., 1989). They found reduced levels of dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC). Experiments using rabbits, mice and guinea pigs showed that dopamine inhibited FDM (Gao et al., 2006; Landis et al., 2016; Mao et al., 2010). Decreased levels of retinal dopamine and DOPAC in FDM were also seen in guinea pigs and rhesus monkeys (Dong et al., 2011; Iuvone et al., 1989). They were also observed in negative lens experiments with chicks but not seen in wild type mice (Guo et al., 1995; Wu et al., 2015). Studies with partial form deprivation using hemifield diffusers, observed a decrease in DOPAC in only the deprived elongated retina (Ohngemach and Hagel and Schaeffel, 1997). Reduced levels of DOPAC were found in the vitreous of chick eyes given a norepinephrine dopamine reuptake inhibitor (Megaw and Morgan and Boelen, 2001). Vitreal DOPAC levels in chicks increased within 3 hours of light onset (Megaw and Morgan and Boelen, 1997). Elevated levels of retinal dopamine, DOPAC and DOPAC/dopamine ratio were seen in eyes of chicks recovering from form deprivation (Pendrak et al., 1997). However, there have been conflicting results in retinal DOPAC levels, as some experiments using myopic defocus showed an increase, while in others the level decreased (Guo et al., 1995; Ohngemach and Hagel and Schaeffel, 1997). Dopamine and DOPAC have been found in the choroid. Choroid and vitreal dopamine concentrations were observed to correlate with retinal dopamine concentrations (Mathis et al., 2022).

Overall, research has demonstrated that in experiments causing axial elongation, dopamine levels are reduced. Dopamine is considered an active participant in the ocular regulation pathway based on the impact of both its agonists and antagonists.

Dopaminergic Retinal Cells

Dopamine is produced in amacrine cells and is synthesized through a series of chemical reactions. L-tyrosine reacts with enzyme tyrosine hydroxylase to produce 3,4-dihyroxy-L-phenylalanine (L-DOPA). L-DOPA then reacts with enzyme DOPA decarboxylase to produce dopamine. Dopamine moves into synaptic vesicles through vesicular monoamine transporter VMAT2 (Iuvone et al., 1978; Kramer, 1971). Dopamine transporters (DAT) are involved in moving dopamine in synapses to dopamine neurons (Mitsuma et al., 1998). As dopamine enters the cell, monoamine oxidase converts dopamine into DOPAC. DOPAC is

(Cohen, Hadjiconstantinou and Neff, 1983). Researchers use DOPAC levels to gauge dopamine levels during experiments (Megaw and Morgan and Boelen, 2001).

In the retina, dopamine has been shown to play a role in the regulation of ocular growth as part of the signal cascade. It has been assumed that there is a transfer of signal from the retina to sclera, with the retina functioning as the key site for dopamine delivery. During FDM, choroidal and scleral dopamine levels remained the same, and it was thought that other non-dopamine molecules were involved in the transfer of signals between the retina and sclera (Ohngemach and Hagel and Schaeffel, 1997). The RPE was also considered a potential site

of action given the presence of dopamine receptors (Rymer and Wildsoet, 2005). Dopamine was released from cultured human RPE (Chen et al., 2011).

D1 versus D2

The D2 receptor has been implicated in the ocular regulation pathway, more so than the D1 receptor. Results from D1 agonists and antagonists have shown minimal reaction, strengthening the case for a D2 receptor pathway. The dopamine receptors are G protein-coupled receptors (Gurevich and Gainetdinov and Gurevich, 2016). The D1 pathway includes D1 and D5 and activates adenylate cyclase and cAMP. The D2 pathway (including D2, D3 and D4), decreases adenylate cyclase and cAMP (Witkovsky, 2004). They also differ in their location within the retina. D1 receptors are present on ganglion, bipolar, horizontal and amacrine cells (Veruki and Wassle, 1996). D2 receptors are located on photoreceptors and RPE (Djamgoz and Wagner 1992; Rohrer and Stell, 1995). Both the apical and basal side of the RPE contain dopamine receptors, D1 through D5 (Rymer and Wildsoet 2005). They are also present on amacrine cells as autoreceptors (Veruki, 1997).

There have been varying outcomes from experiments using the same drug. Differences in experimental paradigm (LIM vs FDM) may impact certain receptor types, thus generating a different response of the same molecule. It may be that both D1 and D2 receptor pathways play some role in ocular growth regulation but more research is needed to confirm this hypothesis.

Animal Studies and Light

Through animal studies, a reduction in FDM was observed with bright light. 25,000 lx was considered bright light and light in the range of 15-630 lx was noted as normal lighting (Smith and Hung and Huang, 2012). Illuminance of 15,000 lx for 5 to 6 hours daily led to a 60% decrease in FDM in chicks while 40,000 lx led to complete inhibition (Ashby and Ohlendorf and Schaeffel, 2009; Karouta and Ashby, 2015). Eyes of rhesus monkeys with FDM had less myopia when exposed to 18,000-28,000 lx (Smith and Hung and Huang, 2012). However, 25,000 lx did not prevent LIM in rhesus monkeys (Smith et al., 2013). It is possible that light is processed differently between FDM and LIM.

Constant light resulted in significant corneal flattening and decreased the anterior chamber depth in chicks. Constant light of 1, 10 or 5000 lx led to light-induced avian glaucoma observed as flatter cornea, smaller corneal diameter, shallower anterior chamber, increased equatorial diameter and weight of the eye (Li et al., 1992). Increased IOP was also noted (Lauber and Boyd and Boyd, 1970). Constant light or dark led to corneal flattening and axial elongation. The type of refractive error was based on length of exposure. If the exposure is short, then hyperopia develops because the cornea flattens quickly, However, with longer exposure, refractive change from axial elongation predominates and myopia develops (Nickla, 2013).

Increase in dopamine release has been linked to light exposure (Cohen et al., 2012). The protective effect of light exposure against axial elongation caused by negative lenses was eliminated by dopamine antagonist, spiperone (Ashby and Schaeffel, 2010). Under photopic

conditions, dopamine levels were elevated in C57BL/6J mice (Landis et al., 2021). Dopamine decreases during constant light. However, it is likely involved in selective pathways as it was shown that constant light prevented FDM but not lens induced refractive changes (Bartmann et al., 1994).

Experiments with chicks given direct sunlight (30,000 lx), led to decreased axial length and less myopic refractions (Ashby and Ohlendorf and Schaeffel, 2009).

Further studies have assessed the impact of flickering light on ocular growth. Flicker frequency of 10 Hz was found to prevent FDM (Gottlieb and Wallman, 1987). Low frequencies ranging from 0.1 to 5 Hz at 500 lx caused myopia in guinea pigs (Di et al., 2013). Dopamine levels increase as a result of flickering lights at 10 Hz (Rohrer and Iuvone and Stell, 1995). 2 hours of daily strobe at 12 Hz prevented FDM and axial elongation, and led to choroidal thickening (Nickla, 2007). The choroid was observed to thicken at 20 lx with flickering lights at both 1 and 10 Hz. Greater choroidal thickening was achieved with continuous light at 470 lx and vitreal DOPAC also increased the most at the same illuminance. In contrast, retinal and vitreal dopamine were higher with flickering light at 20 Hz than continuous light at 470 lx (Mathis et al., 2023). Guinea pigs exposed to light at 600 lx with 0.5 Hz were found to have increased levels of dopamine and DOPAC in the retina and vitreous and became myopic (Luo et al., 2017). Therefore, dopamine levels rise with bright light and flickering light.

Research studies have shown that bright light and high temporal frequency are protective against myopia. Research in human subjects have also shown similar results. Outdoor time

with sunlight exposure can slow down or stop the onset of myopia in children (French et al., 2013). Also, axial length, myopic shifts and myopic progression were all observed to decrease (Wu et al., 2018). Colour contrast and luminance also impacts accommodation and refraction (Rucker, 2013). Increase in choroidal thickness was observed in studies of young adults shown 500 lx in the morning for 30 minutes for 1 week (Read et al., 2018). The mechanism of action to explain the impact on myopia with outdoor exposure is not yet known.

Chapter 6. More Recent Explorations in Dopamine and Eye Growth

Researchers speculated that different results from drug experiments were due to the visual paradigm that was used in the experiment. Complete inhibition of the protective effect of daily vision with spiperone was observed with FDM (McCarthy et al., 2007), whereas only a partial response was obtained with negative lenses (Nickla et al., 2010). To determine if the optical intervention was effecting outcomes, an experiment using spiperone and daily vision with diffusers or negative lenses was designed. Again, spiperone blocked the protective vision response in FDM eyes but not in eyes wearing negative lenses. Therefore, it is likely that there are separate dopaminergic pathways responding to diffusers and negative lenses (Nickla and Totonelly, 2011).

Genetic manipulation through the use of transgenic and knockout mice has allowed for a greater understanding of myopia and dopamine (Chakraborty et al., 2015). In the mouse model, D1 receptor activation has been linked to hyperopia and D2 to myopia (Zhou et al., 2017). Unlike chicks, wild-type mice did not show decreased levels of retinal dopamine after FDM (Chakraborty et al., 2015). An experiment was designed to examine the impact of daily injection compared to continuous infusion of apomorphine in normal and FDM mice. Apomorphine decreased the development of myopia in mice with form deprivation with daily injection but not continuous infusion. As a result, the drug dosing format may influence the results of myopia experiments and should be taken into consideration (Yan et al., 2015).

Prior studies hypothesized that dopamine levels changed depending on the experimental paradigm (Guo et al., 1995). As dopamine related experiments yielded

conflicting results, additional research was needed to

diurnal rhythms and refractive changes. Over a 24-hour period, vitreal DOPAC levels were measured to determine how dopamine levels changed throughout the course of the day. It was shown that vitreal DOPAC levels decreased in response to negative lenses, form deprivation and positive lenses after 24 hours in chicks. FDM or defocus (myopic or hyperopic) or untreated eyes, had diurnal fluctuations in vitreal DOPAC levels. Eyes with 2 hours of daily hyperopic defocus in either the morning or mid-day had noted reduced DOPAC levels during entire light cycle (Nickla et al., 2020). Further research is necessary to understanding how diurnal rhythms effect the role of dopamine in regulating ocular growth.

Research has also focused on the spectral range of light and its possible influence on the development of myopia. However, further studies were necessary to assess the impact of specific wavelengths of light on dopamine levels. Chicks that were exposed to blue or UV lighting had decreased amount of deprivation myopia compared to those under red and white light. Eyes with normal vision that were shown blue light or UV lighting had increased hyperopia. Retinal dopamine increased when either red or blue or UV lighting was used (Wang et al., 2018).

Intravitreal injections of atropine have been shown to increase vitreal dopamine levels in chicks (Mathis et al.,2020). In a study using myopic C57BL/6J mice, the effect of dopamine through the use of atropine was used to assess its impact on choroidal neovascularization. Topical atropine decreased laser induced choroidal neovascularization in mice by decreasing VEGFA, through increased expression of D2 receptors and decreased expression of D1 receptors (Ji et al., 2023). Therefore, not only is atropine involved in

decreasing myopia progression, it also could help prevent the vision related complications from myopia.

Several molecules have been implicated in the retinoscleral signaling cascade including all-trans retinoic acid (atRA). atRA is derived from Vitamin A and has several functions in the eye (Cvekl and Wang, 2009). Further research was designed to examine how atRA levels changed in various ambient lighting, and how atRA and dopamine effect each other. In mice, it was found that ambient light effects dopamine and atRA levels, with longer periods of bright light leading to decreased atRA. Intraperitoneal injections of LDOPA caused transient decrease in the retinal atRA. Thus, it is possible that dopamine could signal atRA downstream in the signal cascade (Talwar and al., 2025).

Chapter 7. Conclusion

The search for a cure for myopia has become imperative as rates skyrocket around the world. The current spectacle lens, contact lens and pharmacological treatments have shown promising results. Animal research has been instrumental in developing an understanding of the myopia model. Form deprivation and spectacle lens experiments have proved that the eye will make modifications based on visual experience. FDM and negative lens lead to ocular elongation and choroidal thinning. These responses are consistent between some animals, despite differences in anatomy. This indicates a similarity in visual processing of FDM and hyperopic defocus in some animals. However, in certain drug studies using FDM and negative lenses, different responses were generated in the same animal. The discovery of choroidal thickness changes during visual manipulations, has led to significant work unraveling the anatomy, neural connections and mechanisms of action of the choroid.

Ocular growth regulation is not only controlled by the brain, but the eye itself has regional control and communication exists between the retina and sclera. Therefore, it is likely that a signalling pathway exists from the retina to the sclera that controls the changes in each layer of the eye. A number of molecules have been proposed to play an active role in myopia. It is possible that a combined interaction between these molecules are responsible for the changes. Nitric oxide, acetylcholine and dopamine are considered to be key neurotransmitters with probable connections to ocular growth regulation. Understanding the role of these molecules in the retinoscleral signaling pathway could unleash new possible myopia treatment options, some that could be more rapid and effective.

There has been significant amount of research dedicated to uncovering the neural network involved in converting visual stimuli to ocular growth. Experiments have shown that dopamine related agents lead to changes in choroidal thickness and axial eye length in a number of animal models. Dopamine has been shown to decrease FDM and LIM. It has led to choroidal thickening. High frequency and bright light caused an increase in dopamine levels. Dopamine agonists prevented FDM and LIM. In chicks, retinal dopamine is decreased by images that are of low luminance or contrast, which leads to myopia (Feldkaemper et al., 1999). Yet, there still exists uncertainties
regulation.

Recent studies have alluded to dopamine within the choroid having a role in the signaling pathway. This could be achieved by the signaling molecules on basolateral side of the

RPE (Mathis et al., 2023). Both choroidal and scleral thickening were noted after intravitreal injections of apomorphine and atropine (Mathis et al., 2025). Recently, dopamine immunoreactivity was identified in small choroidal cells and intrinsic choroidal neurons (Konwar et al., 2025).

Given the extensive research on dopamine, a large scale global clinical trial in human subjects should be initiated to determine if there is in fact a role for dopamine related drugs in the management of myopia. It remains critical for early monitoring of refractive error. Given the current levels of myopia prevalence in Singapore, government officials along with vision scientists and doctors, should develop a collaborative early screening and treatment protocol for newborns. Success in providing early treatment should eventually slow down

progression and decrease risk of myopia related complications. As a majority of experimental paradigms use very high powered lenses, myopia control lenses with peripheral power should be designed to include higher peripheral power. Currently, the DIMS lens has +3.5 power in the peripheral lenslets. Designing lenses with lenslets of +5 or other higher plus power, could allow for more aggressive treatment in rapidly progressing cases.

The complexities of myopia are apparent, but as research progresses, hopefully one day we will be able to find a treatment that not only slows down myopia, but prevents progression.

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