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Circadian rhythms, refractive development, and myopia

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Abstract

Purpose—Despite extensive research, mechanisms regulating postnatal eye growth and those responsible for ametropias are poorly understood. With the marked recent increases in myopia prevalence, robust and biologically-based clinical therapies to normalize refractive development in childhood are needed. Here, we review classic and contemporary literature about how circadian biology might provide clues to develop a framework to improve the understanding of myopia etiology, and possibly lead to rational approaches to ameliorate refractive errors developing in children.

Recent findings—Increasing evidence implicates diurnal and circadian rhythms in eye growth and refractive error development. In both humans and animals, ocular length and other anatomical and physiological features of the eye undergo diurnal oscillations. Systemically, such rhythms are primarily generated by the 'master clock' in the surpachiasmatic nucleus, which receives input from the intrinsically photosensitive retinal ganglion cells (ipRGCs) through the activation of the photopigment melanopsin. The retina also has an endogenous circadian clock. In laboratory animals developing experimental myopia, oscillations of ocular parameters are perturbed. Retinal signaling is now believed to influence refractive development; dopamine, an important neurotransmitter found in the retina, not only entrains intrinsic retinal rhythms to the light:dark cycle, but it also modulates refractive development. Circadian clocks comprise a transcription/translation feedback control mechanism utilizing so-called clock genes that have now been associated with experimental ametropias. Contemporary clinical research is also reviving ideas first proposed in the nineteenth century that light exposures might impact refraction in children. As a result, properties of ambient lighting are being investigated in refractive development. In other

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areas of medical science, circadian dysregulation is now thought to impact many non-ocular disorders, likely because the patterns of modern artificial lighting exert adverse physiological effects on circadian pacemakers. How, or if, such modern light exposures and circadian dysregulation contribute to refractive development is not known.

Summary—The premise of this review is that circadian biology could be a productive area worthy of increased investigation, which might lead to the improved understanding of refractive development and improved therapeutic interventions.

Keywords

circadian rhythms; clock genes; dopamine; melanopsin; myopia; refractive development

Introduction

Despite numerous investigative approaches, much speculation, and continuing controversy extending over several centuries,[1] the etiology of refractive errors remains poorly understood. While clinicians and researchers have accumulated information, the field lacks a validated, broad biological framework to conceptualize the postnatal optical development of the eye. This review will concentrate on myopia (i.e., nearsightedness) because its prevalence is high, it is associated with significant ocular complications, and most recent research addresses mechanisms for myopia development as distinct from hyperopia (i.e., farsightedness). Importantly, considerable literature suggests that the mechanisms responsible for myopia vs hyperopia are not just reciprocal, but may be different.[2–4]

We shall discuss how advances in the understanding of circadian biology may relate to the puzzle of myopia etiology, reviewing ocular rhythms related to eye growth and refractive development and describing pertinent retinal biochemistry and molecular biology. We shall briefly summarize the expanding literature on how ambient lighting and modern behaviors contribute to circadian dysregulation in contemporary societies, and how circadian dysfunction is now increasingly recognized as contributing adversely to systemic health. We propose that applying concepts from modern circadian biology to eye development may provide the broad biological framework needed for a better understanding of myopia causality, and may lead to novel clinical therapies more efficacious than those currently available.

Clinical myopia results from the axial length of the eye exceeding the focusing power of the cornea and the lens, and thus the focal plane of distant objects is imaged anterior to the photoreceptors. Commonly, though not exclusively, myopia is due to excessive axial growth of the eye during childhood. Most distressingly, the incidence of myopia in children and young adults is increasing, especially in developed societies. Prevalence rates are particularly high in some urban areas of East Asia where 80%–90% or more of late adolescents have myopia. These high prevalences in East Asia developed relatively recently, often over just several decades.[5–8] The prevalence of myopia in Western countries is somewhat lower but is still increasing in many areas.[9–11] Current projections estimate that almost half of the world's population may be myopic by 2050.[12] Besides image defocus, clinicians have long recognized that myopia predisposes to many blinding conditions in

adulthood, as reviewed elsewhere,[1,13] including retinal detachment, various retinal and macular degenerations, open-angle glaucoma and forms of cataract. Besides visual blurring, myopia also ranks as a leading risk factor for acquired blindness later in life because of these associated diseases.

Complex interactions between genetics and the environment have long been hypothesized to contribute to the development and progression of myopia. Contemporary genetics offers the prospect of identifying specific regulatory pathways underlying the development of ametropias.[14–16] To date, genetic linkage studies, genome-wide association studies, candidate gene studies, and meta-analyses have associated dozens of genes and gene variants with non-syndromic myopia.[17,18] However, only some of these genes have been replicated in diverse population groups; furthermore, identified genes tend to exert only small effects, typically accounting for only a small proportion of myopia. It has proved difficult to implicate these genes in pathways identified in animal models, and much of the heritability of myopia is unexplained.[14,19] Despite extensive efforts, the expanding, and at times, bewildering, gene lists emerging from contemporary analyses have not yet explained the rapidly increasing prevalence rates, and do not yet identify a path to develop approaches to lessen the adverse clinical impacts of myopia. Evidence best supports a role for inheritance in syndromic and high myopia (see Wojciechowski and Cheng,[20] for review). For low and moderate myopia, as well as so-called ‘school myopia,’ however, it has been argued that features of modern environments, rather than genetics, may exert the major influence underlying myopia and its increasing prevalence in many areas of the world.[15,21]

The environmental parameters responsible for myopia, however, are far from clear. The non-genetic factors most consistently linked with myopia are higher socioeconomic status, higher scores on intelligence tests, higher levels of educational achievement, urban setting, and reduced time outdoors[14,22–25]; but an explanation of how these factors might lead to the biological effect of ocular enlargement remains obscure. Extensive use of the eyes for near tasks (e.g., reading), with the physiologic requirement for accommodation, has long been postulated to cause myopia. [26] However, modern epidemiological methods have yielded inconsistent and sometimes negative associations of near work with subsequent myopia. [14,23–25] Topical pirenzepine, a muscarinic antagonist that does not block accommodation, slows myopia progression in children.[27,28] Experimentally, an accommodative mechanism for myopia seems increasingly unlikely even though the mechanisms of myopia in animal models may not be identical to those occurring in children. As examples, experimental myopia develops after ciliary ganglionectomy to denervate the ciliary muscle,[29,30] and myopia can be induced in squirrels that lack accommodative capacity.[31] In contrast to the muscarinic pharmacology of the smooth intraocular muscles of mammals, the intraocular muscles of birds are striated, [32] and atropine is well-known to not block the nicotinic mechanism underlying accommodation in birds,[33–35] which contrasts to the cycloplegic effects of atropine in children.[36] Atropine blocks experimental myopia in chicks without affecting their intraocular muscles.[37,38] The lack of cycloplegia with potent anti-myopia effects in birds supports a non-accommodative role in the mechanism of myopia, and provided the justification for the clinical pirenzepine studies discussed above.[37] Finally, asymmetric vitreous cavity growth can be induced from local image distortions to specific

retinal regions, but accommodation occurs symmetrically, and, therefore, would be unable to induce observed asymmetric vitreous cavity growth.[39]

The notion that light exposure might explain myopia etiology is now generating much interest.[14,40] It was first postulated in the 19th century that inadequate lighting and/or reduced outdoor activities might be environmental factors contributing to myopia.[41–45] Experimental myopia in several vertebrate species is reduced when animals are reared under bright laboratory lighting (e.g., 10 000–40 000 lux).[46] In children, most, though not all, cross-sectional surveys and prospective studies find an anti-myopia effect of increasing outdoor exposure.[47–49] Despite the statistical significance of the positive studies, however, the magnitudes of the favorable effects of increasing outdoor time in children are fairly modest overall, even if the protective effect is possibly meaningful in some children. For example, increasing outdoor exposure has been shown to exert a 9% reduction for myopia onset.[48,49] Increased outdoor exposures may reduce myopia progression, but available estimates are approximately 0.2 diopters/year reduced progression.[47–49] Outdoor sporting activities do not seem related to myopia inhibition.[50] The protective mechanism of the outdoors is now assumed to be the intensity of outdoor lighting, compared to indoor lighting. Increased release of retinal dopamine, a retinal transmitter repeatedly linked to refractive development,[4] is commonly hypothesized as a mechanism to explain the anti-myopia effects of the outdoors. In chicks, however, outdoor rearing resulted in only a transient inhibition in the progression of experimental myopia.[51] The retinal and vitreous levels of dopamine and its principal metabolite DOPAC (3,4-dihydroxyphenylacetic acid) varied between tissues, eyes and cohorts; and this variability precluded identifying a consistent effect of the outdoors on dopamine or DOPAC. A robust marker, DOPAC was consistently depressed in the retina and vitreous of myopic eyes relative to their contralateral control eyes, similar to findings in myopia of chicks reared indoors. Thus, the effects of outdoor rearing on retinal dopamine metabolism were consistent with myopia, and not its inhibition,[51] suggesting that a mechanism for any anti-myopia effects of outdoor exposure is more complicated than currently conceived.[52] Vitamin D has been investigated as a potential mediator of the effects of time outdoors on myopia. The Avon Longitudinal Study of Parents and Children showed that vitamin D was a biomarker for time outdoors, but it was not independently associated with future myopia.[53] Additionally, analysis of subjects with genetically determined low vitamin D levels uncovered no evidence of an association between serum vitamin D and refractive error.[54] It is unknown if the duration or the timing of outdoor exposure in children, or some other feature of the complex nature of outdoor light,[51] should be considered in future clinical investigations.

Circadian clocks and melanopsin

Circadian rhythms are biological variations with a period of approximately 24 h. They are generated by circadian clocks, which are autonomous cell-based molecular timing mechanisms. Circadian clocks regulate daily rhythms of sleep and alertness, blood pressure and heart rate, locomotor activity, hormone secretion, body temperature, metabolism, and many other physiological processes. Most of these rhythms are controlled directly or indirectly by the ‘master clock’ in suprachiasmatic nuclei (SCN) of the hypothalamus. [55]

The clock mechanism generates daily rhythms of neuronal firing rate in the SCN and surrounding hypothalamic relay nuclei to control rhythmic physiology.[56]

Circadian rhythms and the molecular basis of circadian clocks

The molecular basis for circadian clocks consists of overlapping transcriptional–translational feedback loops (TTFL) involving a conserved set of 'clock genes' (Figure 1; for a recent review, see Takahashi[57]). Central to these feedback loops are two basic-helix-loop-helix PAS domain transcription factors Clock (Cl) and Bmal1 (B). Clock and Bmal1 heterodimerize and bind to E box elements in the promoters of the cryptochrome (*Cry1* and *Cry2*) and period (*Per1, Per2* and *Per3*) genes to activate their transcription. The protein products of the *Cry* and *Per* genes heterodimerize and complex with casein kinase 1 (CK1), which phosphorylates PER. The resulting complex translocates into the nucleus where it inhibits Clock/Bmal1-mediated transcription of the period and crytochrome genes. The temporal delay between transcription and translation combined phosphorylation, nuclear import, and proteasomal degradation results in daily rhythms of the transcripts and protein products of the period and cryptochrome genes. A second TTFL involves activation of the *Rev-erb-a* (RE) and *Rora* (R) genes by Clock/Bmal1. The protein products of these genes drive rhythmic Bmal1 expression through binding to the Rev-erb/Ror elements (RER) in the *Bmal1* promoter. The output of clock is, in part, through clock-controlled genes (CCGs). Many CCGs have E box elements in their promoters that are rhythmically activated by Clock/Bmal1.

Npas2 is a paralog of *Clock*.[59] Like *Clock*, *Npas2* heterodimerizes with *Bmal1* and activates circadian E boxes. Both *Clock* and *Npas2* are expressed in the cells of SCN, where they have overlapping roles.[60,61] Knocking out only one of the genes encoding these transcription factors does not disrupt circadian rhythms in the SCN; the double knockout is required. Coupled with the multiple period and crytochrome genes, these observations indicate that there is considerable redundancy built into the circadian molecular clock to ensure it keeps on ticking.

Peripheral circadian clocks

Prior to the early 1980s, vertebrate circadian rhythms were thought to be generated solely by the SCN.[62] However, in 1983, evidence was presented demonstrating the presence of circadian clock(s) in the eye of *Xenopus laevis* that is/are independent of the SCN, generating a rhythm of the melatonin-synthesizing enzyme, serotonin *N*-acetyltransferase. This rhythm persists for several days in constant darkness and can be entrained by light *in vitro* in *Xenopus* eye cups maintained in organ culture.[63] Subsequently, it was shown that isolated *Xenopus* photoreceptors generate rhythms of melatonin release that can be entrained by light or dopamine and persist for several days in constant darkness, providing definitive evidence for an autonomous circadian clock in photoreceptors.[64,65] Circadian rhythms of melatonin release have also been observed in mammalian retina,[66] as well as many non-mammalian species. It is now clear that many aspects of retinal physiology are under the influence of circadian clocks (Figure 2; for a recent review, see McMahon *et al.*[67]).

Circadian clock genes are found in many retinal cell types, including RPE, bipolar cells, horizontal cells, amacrine cells, ganglion cells, and Müller glial cells, as well as in photoreceptor cells,[68–74] particularly cones.[75] The clocks in the retina use the same set of clock genes expressed in the SCN,[76–79] although there appears to be less redundancy than in the SCN.[80]

Dopamine, a putative regulator of refractive development, [81–83] appears to play a particularly important role in the retinal circadian system. Clock genes are highly expressed in dopamine amacrine cells.[68,84] Dopamine entrains circadian rhythms of gene expression in RPE, photoreceptors, and retinal ganglion cells,[79,85–89] as well as the inner retinal rhythmic expression of the circadian reporter Per2 luciferase.[90] Disruption of dopamine signaling disrupts circadian rhythms of cone ERG responses, contrast sensitivity,[79,85] and protein phosphorylation in photoreceptor cells.[91–93] Dopamine regulates connexin-36 gap junctions in the inner and outer retina.[93,94] Interestingly, polymorphisms in the gene that encodes connexin-36, *GJD2*, have been associated with myopia in genome-wide association studies.[95,96] With the presumed role of retinal dopamine in refractive development discussed below,[81–83] findings suggest that interaction between dopamine and retinal circadian clocks may influence refractive development and myopia.

Melanopsin

In the 1990's, a series of studies revealed that rod and cone photoreceptors were not required for photoentrainment of circadian rhythms of locomotor activity in mice,[97–99] providing evidence for a non-rod, non-cone ocular photoreceptor. Subsequently, an opsin that regulates light-induced dermal melanophore migration in *X. laevis* was discovered and termed melanopsin.[100] This opsin is more closely related to cephalopod opsins than to rod and cone opsins, suggesting an ancient evolutionary origin. It was found to be expressed in the *Xenopus* eye, as well as in the skin. In non-mammalian vertebrates, such as chicks, melanopsin is expressed in several retinal cell types. There are two forms of melanopsin, designated Opn4x and Opn4m due to sequence similarity to the Xenopus and mammalian genes, respectively.[101] A human homolog of melanopsin has been cloned (gene symbol *OPN4),* and found to be exclusively expressed in a subpopulation of retinal ganglion cells,[102] commonly referred to as intrinsically photosensitive retinal ganglion cells (ipRGCs).[103] The ipRGCs are directly photosensitive, [104] through the activation of melanopsin, and some axons project directly to the SCN.[105,106] Unlike rod and cone photoreceptors, which hyperpolarize in response to light, ipRGCs show a depolarizing response to light similar to photoreceptors of invertebrates. Melanopsin is a vitamin A-based photopigment, like the rod and cone opsins, but with a distinct action spectrum with maximum absorption at 484 nm (blue).

In addition to innervating the SCN to photoentrain circadian rhythms, ipRGCs influence retinal signal processing via retrograde signals. For example, the diurnal rhythm of the photopic ERG observed in wildtype mice is absent in melanopsin knockout (*Opn4*$^{-/-}$) mice. ipRGCs appear to synapse with dopamine amacrine cells and increase their activity,[107–109] providing a light-driven centrifugal signal to the inner retina. Furthermore, elimination of ipRGCs attenuates light adaptation in the cone ERG, and this effect is reversed by treatment

with a dopamine receptor agonist. [109] The synapses between ipRGCs and dopamine amacrine cells may be reciprocal, as dopamine appears to regulate melanopsin expression. [110] Collectively, these studies suggest that ipRGCs and melanopsin could influence the retinal pathways contributing to refractive development.

Another recently identified opsin, neuropsin (Opn5), is expressed in another subset of retinal ganglion cells.[111] Neuropsin has been shown to play a role in the photoentrainment of retinal circadian clocks, but not the clocks in the SCN. Thus, neuropsin is another candidate for regulating rhythms of eye growth and refractive development.

Alterations of clock genes and clock-related genes in experimental myopia in chicks

A transcriptome analysis of the effects of 6 h of hyperopic defocus with a −15 D lens in chicks identified several classes of differentially expressed genes in combined retina and retinal pigment epithelium (RPE), including genes related to glutamate, GABA, glycine, and acetylcholine neurotransmission. [112] In addition, the expression of several circadian clock genes and clock-related genes was down-regulated. These included *Clock* (circadian locomotor output cycles kaput), *Cry1* (cryptochrome 1), *Npas2* (neuronal pas domain protein 2), *Per3* (period homolog 3), as well as *Mtnr1a*, which encodes the type 1 melatonin receptor, and melanopsin *(Opn4).* These genes were unaffected by myopic defocus with a +15 D lens.

In another study, comparing the effects of form-deprivation in indoor-reared and outdoor-reared chicks revealed changes in the expression of clock genes in combined retina/RPE samples after 3 days of form-deprivation.[51] As in other assays of experimental myopia,[13] the magnitude of the altered retinal/RPE gene expression between goggled and non-goggled eyes was small in cohorts reared indoors or outdoors, regardless of chick age. Besides the small magnitude of the effects, there were also variabilities in the gene expression changes between cohorts, hampering generalized conclusions. Nonetheless, the expression of each of the assayed genes was affected under one or more conditions. These measurements were made at a single time of day, and it is unknown if rhythms of clock gene expression are affected by myopia-producing stimuli. Retina and RPE were not separated for analysis in these reports, and it is possible that the neurosensory retina and RPE contribute differently to the altered expression of clock or circadian rhythm-related genes, as recently seen for *Opn4* in tree shrew eyes after minus lens wear.[113]

Potential involvement of the endogenous retinal clock in refractive development

Animal models of myopia are useful for isolating potential circadian rhythm effects from other factors modulating refractive development. Besides assaying clock and circadian rhythm-related genes just discussed, another approach is directly assaying the contributions of endogenous retinal clocks in refractive eye growth by investigating mice with genetic elimination of specific retinal clock genes. Due to the critical nature of clock genes and normal circadian rhythms, systemic knock-outs of intrinsic clock genes can reduce survival and cause other confounding metabolic abnormalities.[114,115] Thus, retinal-specific knock-outs would be most advantageous to study. To date, we are only aware of results from retinal-specific *Bmal1* knock-out mice with normal visual input in which the refractive error

was significantly more myopic than wild-type mice across age, with longer axial length and vitreous chamber depth, but shallower anterior chamber depth.[116] Interestingly, these changes are similar to those seen in chicks reared in constant light,[117] a condition also known to exert intensity dependent effects on the circadian period,[118] and conforming to a hypothesis that lighting effects on refractive development might relate to effects on the circadian clock.

Initial direct investigations of melanopsin in refraction

As mentioned above, time outdoors and increased light exposure have been shown to be protective against myopia in children,[47,119] and increased light intensity inhibits form-deprivation myopia in animals.[120,121] Studies have demonstrated that increased light exposure leads to an increase in retinal dopamine,[122] which may, in part, be mediated by synaptic connections between ipRGCs and dopaminergic amacrine cells.[123] Additionally, ipRGCs are spectrally tuned to short wavelength light with a peak sensitivity around 484 nm,[124] which is a prominent wavelength in sunlight. Evidence from these studies suggest a potential role for melanopsin in refractive development.

To examine the contribution of melanopsin to normal refractive development and form-deprivation myopia in mice, a melanopsin knock out mouse (*Opn4*$^{-/-}$) was utilized. [125] When raised under normal visual conditions, *Opn4*$^{-/-}$ mice were significantly more myopic at 4 weeks, then more hyperopic by 16 weeks, compared to wild type mice. Additionally, *Opn4*$^{-/-}$ mice undergoing form-deprivation were significantly more myopic than wild type animals. These results suggest that melanopsin signaling pathways contribute to both normal refractive development and form-deprivation myopia in mice. However, the mechanism by which melanopsin interacts with refractive development has yet to be elucidated.

The influence of monochromatic light on refractive status has been evaluated in guinea pigs to understand the role of melanopsin in myopia.[126] Animals raised in short wavelength blue light (480 nm, peak sensitivity of melanopsin ganglion cells) were approximately 2 D less myopic than those raised in medium wavelength green light (530 nm, peak sensitivity of the guinea pig medium wavelength cone). Additionally, animals raised in blue light had decreased melatonin concentration in the pineal gland than those raised in medium wavelength light. The authors found that melanopsin-immunolabeled cells, melanopsin mRNA and protein were increased in animals that were raised in blue light compared to green light. While these results do not directly implicate melanopsin as having a role in the observed decrease in myopia with blue light, further investigations are required to understand the influence of ipRGCs in myopia.

A primary role for ipRGCs is photic regulation of melatonin release from the pineal gland. [127] Recent studies have found that myopia may contribute to decreased sleep quality in humans.[128,129] Jee *et al.*, found an inverse relationship between sleep duration and myopia in Korean adolescents.[129] Similarly, another study reported that children with high myopia exhibited the poorest scores on the Pittsburgh Sleep Quality Index (PSQI), a sleep quality questionnaire. [128] The authors attributed the observed decreased sleep quality to high demands in school, distress over poor vision, or decreased ipRGC function in myopic eyes. Sleep, circadian rhythm, and ipRGC activity have also been shown to be affected in diseases

which affect the inner retina, such as glaucoma,[130] and in outer retinal diseases, including age related macular degeneration.[131] Another study reported a positive association between morning melatonin concentration and the magnitude of myopia, with myopes demonstrating up to three times greater melatonin concentration than non-myopes.[132]

Adhikari and colleagues evaluated the post-illumination pupil response in human subjects, [133] and found no associations between refractive error and the ipRGC inputs to the pupil control pathway. However, another investigation found a significant positive correlation between a more hyperopic refractive error and a slower rate of pupil redilation to 0.1 Hz flashing stimuli, which varied as a function of light exposure over the previous 5 days.[134] Conflicting results and current interest in light exposure and eye growth warrant further investigation into the role of melanopsin in refractive error development and potential relationships between light exposure, myopia, and the ipRGC-driven pupil responses.

Ocular diurnal rhythms and eye growth

Following initial observations by Jensen and Matson,[135] Lauber and colleagues investigated the effects of constant darkness or constant light on ocular growth in chicks.[136,137] Discovery of elongated eyes and flat corneas in chicks exposed to continuous light led to the hypothesis that the absence of normal diurnal cues (e.g., the light/dark cycle) may alter ocular diurnal rhythms, resulting in abnormal eye growth and refractive error development. Over the ensuing decades, some progress has been made towards understanding the role that ocular diurnal (or circadian) rhythms play in the process of emmetropization, and accordingly, in the development of ametropias.[138] This section will focus on diurnal rhythms in axial length, choroidal thickness, scleral biosynthesis rates, and intraocular pressure (IOP), and discuss their potential influences on ocular growth and refractive error development in humans and animal models.

Natural diurnal variations in axial length and choroidal thickness

Diurnal variations in axial length of the eye were first reported by Weiss and Schaeffel,[139] who found that eyes of young chicks grow during the day and ‘shrink’ at night. Axial length was measured as the distance from the anterior cornea to the RPE. This finding was corroborated and expanded upon by two later studies,[140,141] one of which, by using more frequent measurements, showed that the acrophase (rhythm peak) occurred in the afternoon. [140] Perhaps more importantly, the better resolution afforded by higher frequency ultrasonography[140] and non-contact laser interferometry [141] made possible the discovery that the thickness of the choroid also showed diurnal oscillations, thickening during the night and thinning during the day, in approximate anti-phase to the rhythm in axial length (Figure 3). Thus, the night-time shortening of eye length, or at least part of it, was a result of the choroidal thickening. These rhythms persisted in constant darkness in chick for at least three cycles; hence, they are endogenous, or driven by a clock.[142]

These biometric rhythms were also found in a primate, the common marmoset.[144] In young juvenile marmosets, the phases of the two rhythms were similar to those of chicks, with the axial rhythm peaking in the daytime, and the choroidal rhythm peaking at night, in approximate anti-phase. However, in older marmosets, the axial length rhythm peaked at

night instead of day, resulting in the two rhythms being in-phase. This phase-relationship difference between the two age groups was hypothesized to be related to differing ocular growth rates; in slow-growing chick eyes that were responding to myopic defocus induced by positive spectacle lenses, the rhythms were in-phase as well, similar to that of the older, slower-growing monkey eyes.[143]

The evolution of precise, non-contact techniques, such as the partial coherence interferometry (PCI) and optical coherence tomography (OCT), has allowed changes in axial length and choroidal thickness of the human eye to be measured accurately at a micron level. Studies utilizing PCI have shown that the axial length of human eyes, across various ages (7–53 years), undergoes significant diurnal variations (Figure 4).[145–148] Similar to findings in different animal eyes, the axial length of the human eye is typically longest during the midday and shortest at night, with an average magnitude of diurnal variation of around 25–45 μm.[146,148] Furthermore, a study that measured ocular diurnal rhythms over two consecutive days (at 3 h intervals from 9:00 am to 9:00 pm each day) found the magnitude and timing of rhythms to be similar between age-matched adult myopic and emmetropic subjects (mean age, 25 years).[148] The mean diurnal change in axial length equates to approximately 0.06 to 0.11 D in human eyes,[149] which is a visually and clinically insignificant shift in focus. However, these findings demonstrate that rhythms are conserved across species, and thus may play an important role in regulating normal ocular growth in humans, similar to chicks and marmosets.[138]

There have been only limited investigations into diurnal variations of the choroid in human eyes. Brown *et al.*, in a re-analysis of existing PCI data, reported the first evidence of diurnal variations in choroidal thickness of human subjects. [150] They found the diurnal fluctuations in choroidal thickness to be in approximate anti-phase to that of axial length. Since then, a number of studies using the PCI and OCT have confirmed diurnal variations in choroidal thickness, with the choroid being thickest during the night and thinnest during the day, having a mean diurnal amplitude of about 30 μm (Figure 4).[148,151,152] With a mean subfoveal choroidal thickness of approximately 250, 30 μm corresponds to an approximately 12% change, resulting in a small refractive effect of about 0.18 D.[148] Similar to animal eyes, the average phase of the longest axial length coincides with that of the thinnest choroid, and vice versa (i.e. peaks of the two rhythms are anti-phase by about 12 h)[148]; the magnitude and phase of these fluctuations are similar between adult myopes and emmetropes.[148] Future studies are required to examine the phase associations in young progressing myopic and emmetropic children to better understand the relationship between ocular diurnal rhythms and refractive error development.

Effects of altered visual environment on diurnal variations

One of the crucial findings from Weiss & Schaeffel was that depriving the eye of form vision, which results in excessive elongation and myopia, altered the rhythm in axial growth so that instead of ‘shrinking’ at night like eyes with a normal visual experience, eyes grew at night as well as day, appearing to abolish the diurnal rhythm.[139] This observation was the first concrete evidence since earlier constant light studies[135–137] that ocular diurnal rhythms may be involved in eye growth regulation. However, while it was true that the deprived eyes

were indeed growing faster at night, the rhythm in axial length was not abolished. Measurements at 6 h intervals showed that the rhythm was intact but phase-shifted by a few hours, bringing the axial length and choroid rhythms into exact anti-phase.[140] Stronger evidence for an association between alterations in ocular growth rate and alterations in rhythm phase was that slowing growth by imposing myopic defocus with positive lenses caused a phase-delay in the axial rhythm and a phase-advance in the choroidal rhythm, thus bringing the two rhythms into phase.[143] In faster-growing eyes wearing negative lenses, the two rhythms were similar to those of (faster-growing) form-deprived eyes. Data from eyes growing at different rates in response to form-deprivation or defocus showed a significant positive correlation between growth rate and the phase difference between the two rhythms, supporting a causal link between the two[143]; however, recent evidence regarding temporal integration properties (see below) has weakened this hypothesis.[153]

The molecular/cellular mechanisms underlying the diurnal changes in choroidal thickness, and how these might impinge on scleral growth, are unknown. It is likely that the choroid responds to upstream signals from the retina and/or RPE, but whether these choroidal responses involve thickness-dependent (and hence diurnal-dependent) release of growth factors, or whether the choroid acts as a barrier or facilitator to these growth factors depending on its thickness, requires further study. There is evidence that supports both hypotheses. For example, choroidal thickness predicts subsequent ocular growth rate in normal chick eyes, with thicker choroids predicting slower growth, and vice versa, in support of the 'barrier' hypothesis[154] (however, see Guggenheim *et al.*[155]). Furthermore, thicker choroids synthesize more proteoglycans than thinner ones,[156] hence the stiffness of the choroid, and thus the pressure (IOP) drop across it, might influence scleral proteoglycan synthesis in a diurnal manner.[157] In support of the former 'thickness-dependent release' notion, thicker choroids of eyes responding to myopic defocus with decreased growth release greater quantities of retinoic acid than thinner choroids of eyes responding to negative lenses with increased eye growth. Furthermore, exogenous retinoic acid results in a decrease in scleral proteoglycan synthesis *in vitro*.[158] Finally, co-culture of experimentally-thickened choroids with scleral punches results in decreased scleral proteoglycan synthesis.[159] The precise signaling cascade, and exactly how diurnal rhythms in axial length (perhaps involving scleral proteoglycan synthesis), choroidal thickness and IOP interact to regulate ocular (i.e., scleral) growth clearly requires further study, but evidence strongly suggests that they play a crucial role in emmetropization.

The temporal integration dynamics of eye growth differ markedly for myopic vs hyperopic defocus: myopic defocus is more robust, such that the eye slows its growth in response to a few daily hours of exposure. The growth stimulating response to hyperopic defocus induced by negative lenses is thought to require almost the entire day of exposure.[160,161] However, recent evidence showed that a brief, 2 h exposure to hyperopic defocus in chicks given first thing in the morning resulted in a small but significant increase in eye growth.[162] Conversely, if the eye is exposed to myopic defocus in the morning, the growth *inhibition* is significantly *less* than that resulting from defocus at midday.[153] Both 'morning' defocus conditions were associated with abnormal axial rhythms that did not exhibit a 24-h sinusoidal function (Figure 5). These results suggest that eye growth may be most responsive to 'go' signals in the first part of the light cycle, and more responsive to 'stop' signals in the

mid to last half of the light cycle. This may be due to diurnal sensitivities of the retinal defocus 'integrator,' and/or a scleral growth regulator that are perhaps most susceptible to hyperopic defocus early in the day, and to myopic defocus later in the day, or to the potentially diurnally-dependent choroidal responses discussed above. Whether scheduling reading activities at specific times of the day could have a positive impact on school children at risk of developing myopia could be a novel approach to investigate interactions of near work with refractive development.

Defocus-induced phase shifts in axial length and choroidal thickness rhythms occur in humans as well.[163,164] In two different studies, Chakraborty and colleagues investigated the effects of 12 h (9:00 am to 9:00 pm) monocular myopic[163] and hyperopic[164] defocus on ocular diurnal rhythms in adult human subjects. Consistent with observation in chicks, the introduction of +1.50 D of monocular myopic defocus for 12 h reduced the mean amplitude of the diurnal rhythm in axial length, and phase shifted both axial length (phase-delayed) and choroidal thickness (phase-advanced) rhythms of the defocused eye.[163] Conversely, exposure to the same duration of −2.00 D of monocular hyperopic defocus results in a significant increase in the amplitude of diurnal change, but no change in the peak timing of diurnal rhythms in both parameters. [164] The effects of defocus were confined to the defocused eye with no significant crossover effects on the contralateral (untreated) eye. In both studies, the changes in axial length rhythms were approximately anti-phase to choroidal rhythms (peaks separated by approximately 12 h), suggesting that defocus induced changes in axial length may be associated with changes in choroidal thickness. These blur-induced bidirectional changes indicate that ocular diurnal rhythms of human subjects are sensitive to both the presence and sign of imposed defocus. These findings may help understand of the potential role of optical defocus in regulating longer-term ocular growth and refraction in human eyes.

The animal studies mentioned above provide definitive evidence that 'abnormal' visual input that causes changes in ocular growth rate also affects the phase, amplitude and form of the ocular diurnal rhythm curves, and thus support an association between altered rhythms and altered eye growth. Use of constant light[135,136,165] or darkness[166–168] also leads to abnormalities in eye growth, perhaps related to altered rhythms in ocular dimensions because constant light in particular can affect the circadian clock. However, the role of rhythms was not explicitly tested in early studies.

What about exposure to light at night, such that one might experience in modern society? The advent of artificial light, and resultant increase in the use of night-time illumination, including exposures to (predominantly) blue light from computer/video/TV screens, has become a recognized health concern,[169–173] but its potential impact on vision and ocular health has largely been ignored. A retrospective study of 479 children published years before the recent surge of interest in 'light at night' reported a significant association between the use of nighttime lighting in the first 2 years of life and the development of myopia[174] – a controversial finding that was not replicated by other studies published around the same time.[175–178] Nevertheless, in chicks, exposure to a mere 2 h of light at mid-night caused an 'acute' growth stimulation over the 6 h following the illumination, which altered the rhythm in axial length, eventually resulting in longer eyes.[179] Hence, fragmentary evidence from

both humans and animals supports the notion that effects from light exposure, perhaps by influencing circadian rhythms, may underlie the development of ametropias. Future studies are needed to examine the interaction of contemporary patterns of light exposures and rhythms in ocular dimensions in young, progressing myopic children (or children at risk of developing myopia) to better understand the relationship between ocular diurnal rhythms and refractive error development, and to assess the potential of modifying the rhythms as a possible therapeutic target for inhibiting myopic ocular growth in children.

The rhythms in IOP and emmetropization: risk factors for myopia?

While ocular enlargement is an established consequence of elevated IOP in congenital glaucoma,[180] a long-held, but at this point, mostly discredited hypothesis was that common myopia is a result of IOP stretching the sclera, but whether this was due to an abnormally-high IOP, or a weaker-than-normal sclera, was debatable (see Pruitt,[181] for review). While some find higher daytime IOPs in myopes than nonmyopes, [182–186] other reports are contradictory. For example, a prospective study of 106 Chinese children found that in the 13 children who became myopic, IOP was higher after the development of myopia, but not prior to it.[187] Another group followed emmetropic children over a 3 year period and reported that the IOP of children who developed myopia did not differ from those who remained emmetropic.[188] It is notable that most of these studies were limited by non-controlled times of the day for IOP measurements, leaving unresolved the question of whether IOP measured at a single time point is a crucial risk factor for myopia, or whether the amplitude or phase of the rhythm in IOP specifically might impact myopia development. Several studies have addressed this issue by measuring IOP at different times of day in myopic and emmetopic subjects: most report that IOP peaks in the late night/early morning in both (2:00–4:00 am)[189–191]; however, it was inconclusive whether rhythm parameters differed between groups. Two studies found that myopes had a smaller IOP rhythm amplitude.[192,193] By contrast, a prospective study of glaucoma patients with myopia reported no difference in IOP amplitude compared to emmetropes, but myopes had higher daytime IOPs and greater variability in phase.[194] Determining diurnal IOP rhythms in humans using traditional IOP measurement techniques is fraught with confounding issues such as awakening participants for measures. Recent advances in technology have led to the development of novel sensors to measure IOP[191,195] that may provide more comprehensive measurements of habitual diurnal IOP rhythms and further insight into relationships between IOP rhythms and myopia. To date, however, the bulk of evidence weighs against a role for IOP in the development of myopia.

Is there an association between the rhythms in IOP and rhythms in axial length?

All species studied exhibit diurnal fluctuations in IOP, however, their phases and amplitudes differ. In rabbits,[196–198] rats,[199,200] and mice,[201] IOP is lower during the day than at night. By contrast, the rhythm in guinea pigs is more similar to that of humans[191] and monkeys,[202] with an acrophase (peak) in the early morning and a trough after lights off.[203] In the chick, the IOP rhythm shows an acrophase at mid-day and persists in constant darkness, stablishing it as circadian.[157] Notably, the phase and shape of the IOP rhythm in chick is similar to that of the rhythm in axial length (Figure 6), perhaps suggesting that it ‘drives’ the rhythm in length by inflating the eye during the day and relaxing it at night.[140] In support of such a

'mechanical' mechanism, ocular compliance (change in length per change in exerted pressure) is consistent with IOP fluctuations accounting for the changes in length.

However, observed dissociations between the IOP and axial length rhythms weaken this hypothesis. For instance, in form-deprived myopic eyes, the IOP rhythm becomes desynchronized from the light:dark cycle (i.e., show variable acrophases) and hence dissociated from the axial length rhythm which remains 'normal'.[157] Similarly, lesions of the superior cervical ganglion (sympathectomy) markedly reduce the amplitude of the IOP rhythm while having no effect on the rhythm in axial length.[204] Therefore, while a purely 'balloon-like' inflation/deflation mechanism is not supported, an alternate way for the IOP rhythm to influence eye size is that the changing forces exerted on sclera could alter matrix (proteoglycan) synthesis which would eventually lead to changes in eye size.[205] In support of this, the application of mechanical force changes the synthesis of matrix components in connective tissues (see van Kampen *et al.*,[206] for review); furthermore, cyclic changes in force are the most effective at increasing biosynthesis rates.[207] One hypothesis is that the rhythm in IOP influences the rhythm in scleral proteoglycan synthesis, which itself is rhythmic, with an efficacy that is dependent on the phase of the (rhythmic) scleral cell cycle. If so, then the phase at which IOP peaks with regard to one of these other rhythms might determine the effect of IOP on matrix synthesis and hence, ocular elongation, with myopia developing if its peak was coincident with an optimal phase of scleral biosynthethic 'receptiveness' to force. The evidence for a role for scleral biosynthesis in the development of myopia is discussed in the following section.

Scleral rhythms and emmetropization

Because ocular elongation is rhythmic,[139–141] and because eye growth in chicks is influenced by the rate of synthesis of scleral proteoglycans (matrix molecules),[156,208–210] it is plausible that a rhythm in scleral matrix synthesis underlies the rhythm in axial length. From *in vitro* explant cultures of chick sclera harvested at different times of the day, it was found that scleras from normal eyes synthesized more proteoglycans during the morning than at night,[205,211] although scleras from myopic eyes had higher rates of synthesis at all times.[205] More detailed data were obtained from experiments using a flow-through perfusion system that measured the secretion of radiolabeled proteoglycans from chick sclera at 2 h intervals[205]: scleras from normal eyes showed an endogenous 24 h (diurnal) rhythm in proteoglycan synthesis, chiefly chondroitin-6-sulfate, that persisted for at least 3 days in culture. Scleras from myopic eyes were also rhythmic, but Fourier analysis identified the major frequency component to be 1.875 cycles per day (i.e., ultradian), with a secondary diurnal frequency (i.e., 1 cycle per day). Because the phase was strongly re-set by the culture conditions, potential phase differences in synthesis rates between normal and myopic scleras could not be determined. Therefore, while an endogenous circadian rhythm in proteoglycan synthesis in chick sclera contributes to or may even underlie the oscillations in axial length, the lack of a large difference between normal vs myopic scleral rhythms suggests that the excessive elongation in myopic eyes is not a major result of alterations in rhythm parameters in scleral proteoglycan synthesis. However, the strong ultradian oscillations in scleras from myopic eyes might be a contributing factor, perhaps related to the altered (desynchronized) rhythms in IOP in these eyes. These speculations await further study.

In humans, a recent study using anterior segment OCT reported diurnal variations in the thickness of the temporal anterior sclera of young adults.[212] The authors found significant thickening of the sclera in the early morning immediately after waking, and thinning of the sclera during the mid-day, with a mean amplitude of 21 μm. The total scleral thickness (668 μm) and the amplitude of diurnal variation was maximum at the scleral spur (52 μm), compared to regions up to 2.5 mm away from the scleral spur. If or how these diurnal fluctuations in scleral thickness relate to the onset or progression of myopia requires future research.

Retinal signaling in refractive development

Animal models of experimental myopia have revealed that local retinal processing is essential for the response to form deprivation or lens defocus, and presumably normal emmetropization.[39,213] However, the specific retinal electrical and chemical signals that modulate refractive eye growth remain elusive. Here we review retinal circuitry and chemical signaling that may contribute to refractive development and how these are linked to circadian rhythms. Notably, retinal stimulation through the ON pathway of the retina stimulates two key regulators of circadian rhythms, dopamine and ipRGCs.

Retinal pathways relevant to refractive development

Light hyperpolizes the plasma membranes of both rods and cones to stimulate parallel vertical pathways in the retina that lead to activation of ON- and OFF-center ganglion cells (Figure 7). Visual information can travel from the rods to second and third order neurons via three different pathways: (1) Hyperpolarized rods synapse on rod ON bipolar cells causing them to depolarize and release glutamate. The rod bipolar cells synapse onto AII amacrine cells, which also depolarize, and form inhibitory synapses with cone OFF bipolar cells and excitatory electrical synapses with cone ON bipolar cells.[214] (2) Rods form gap junctions with cones,[215] which then activate cone pathways that stimulate ON and OFF pathways. (3) Rods form synapses to OFF bipolar cells.[216] Cone activation by light leads to direct stimulation or inhibition of ON and OFF cone bipolar cells,[214] which make excitatory synapses to ON- and OFF-center ganglion cells. Rods also regulate ON and OFF pathways, but indirectly through the AII amacrine cells. This complex neural network leads to several parallel retinal circuits that stimulate common ON and OFF pathways. Additionally, circadian rhythms modulate which pathways are being used through the opening and closing of gap junctions.[217]

Additionally, ipRGCs can be stimulated directly by activation of the photopigment, melanopsin, or through the traditional rod and cone photoreceptor pathways (Figure 7).[218] The five types of ipRGCs identified in mammals receive predominately ON pathway input.[219] However, they are also unique in sending signals retrogradely from the ipRGCs to the dopaminergic amacrine cells, to potentially facilitate light-adapted vision.[109] In addition to the role in imaging forming vision, ipRGCs also contribute to non-imaging forming behaviors, including the pupil light reflex and circadian photoentrainment.[218,220]

The contributions of these different retinal circuits to refractive development is complex.[221] Evidence for photoreceptor-initiated pathways consists of studies showing that animal

models with cone-dominated retinas have the most consistent and largest responses to experimental myopia (chick and tree shrew). Furthermore, in the chick, rod pathways may be suppressed diurnally,[222] further implicating cone pathways in refractive development. However, another study suggests that the cone-rich fovea is not needed for emmetropization in non-human primates[223]: laser ablation of the fovea in rhesus monkeys did not prevent successful refractive development or the response to form-deprivation.[223] This study suggests that the peripheral retina, which is composed of approximately 5% cones and 95% rods in humans,[224] can control refractive development. However, these studies did not empirically test whether the rods or the cones are driving the response. Studies of mice with selective rod pathway dysfunction [rod transducin (*Gnat1*) mutation] fail to 'emmetropize'; i.e., *Gnat1*$^{-/-}$ mice show no alterations in refractive error across age while wild-type mice shift towards more hyperopic refractions and then plateau at about 6 weeks of age.[225] Furthermore, absence of rod pathway activation prevents the eye from responding to form-deprivation. *Gnat1*$^{-/-}$ mice showed no shift in refractive error even after 8 weeks of goggling while wild-type mice show a −2.54 ± 0.77 D shift by 3 weeks.[225] Rod photoreceptors drive circadian photoentrainment across a wide range of intensities,[226] thus, these effects could be due to loss of circadian rhythms rather than specific rod pathway stimulation. Additionally, cone dysfunction caused by elimination of cone transducin (*Gnat2*) did not alter refractive development with normal visual input, but did increase the susceptibility to myopia (2.5 D diopters greater).[227]

Studies on the contributions of ON and OFF pathways to refractive development and myopia have been relatively few. ON and OFF pathways have been examined in the chick model of form-deprivation myopia using pharmacological blocking agents[228–231] and lens induced myopia using flicker stimulus (moving or stationary pattern stimuli). [232] However, no definitive conclusions have been reached. In a study using kittens, ON pathway blockage with D,L-2-amino-4-phosphonobutyric acid (APB) resulted in more hyperopic refractions and shorter axial lengths.[233] Indirect clinical evidence of ON pathway involvement in modulating refractive eye growth comes from patients with retinopathy of prematurity in which the ON response, as recorded with multifocal ERGs, decreased as the amount of myopia increased (although myopia in retinopathy of prematurity is mainly due to changes in anterior chamber depth and corneal curvature rather than axial elongation). [234] Patients with the complete form of X-linked congenital stationary night blindness (CSNB1), who have a defect that results in loss of ON pathway transmission and not rod function, present with high myopia.[235] In contrast, patients with the incomplete form of X-linked CSNB (CSNB2), in which a calcium channel defect decreases, but does not eliminate, both ON and OFF transmission, do not present with high myopia.[235] More recently, a mouse model with a defect in the ON pathway between rods and ON bipolar cells due to an *Nyx* mutation has been examined. [236–238] *Nob* mice with this mutation have successful refractive development in a normal visual environment,[239] suggesting that visual activation of intact retinal pathways provides feedback for a successful match between eye size and ocular power. However, form-deprivation leads to increased susceptibility to myopia in *Nob* mice, suggesting increased sensitivity to alterations in visual input.[239] Increased susceptibility to form-deprivation was replicated in another ON pathway defect model with an mGluR6 mutation,[240] suggesting that the ON pathway disruption is the important element for

refractive development. Furthermore, the OFF pathway does not appear to be critical for refractive development, as disruption of the OFF pathway caused by *Vsx1* mutation did not significantly alter refractive development or the response to form deprivation.[241]

Direct comparisons of the different experimental paradigms is difficult because it is unknown if the ON pathways is completely blocked or what compensatory mechanisms may have occurred for the loss of function. However, studies in mutant mice that are due to a functional defect in the retina (and not a retinal degeneration) suggest that defects in rod photoreceptor pathways and ON retinal pathways may have larger impacts on the refractive development and/or the susceptibility to experimental myopia (Table 1). However, it is notable that these mutations don't affect refractive development under normal and visual deprived conditions equally, conforming to clinical hypotheses that complex interactions of genetic and environmental factors underlie myopic eye growth. The importance of ON pathway stimulation in refractive development may be due to its influence on circadian regulators, such as dopamine (discussed below) and melanopsin (see Section 2.3). Further work is needed to determine how circadian rhythms may alter these retinal pathways and therefore affect susceptibility of the eye to myopic eye growth.

Classic retinal neurotransmitters and dopamine in refractive development

Transmission of the visual signal through the retinal circuitry requires neurotransmitters and other neuromodulators and neuropeptides. Since transmission is regulated by gap junctions modulated by circadian rhythms and multiple neurotransmitters are modulated by dopamine, it is important to review which neurotransmitters could contribute to refractive eye growth through circadian entrainment, even if the direct evidence of this is currently sparse. Synaptic communication between the vertical pathways in the retina occurs through the release of glutamate. This is the main neurotransmitter between photoreceptor and bipolar cells in both the ON and OFF pathways, acting on metabotrophic and ionotropic glutamate receptors on the ON- and OFF-bipolar cells, respectively. Lateral communication and feedback occurs through GABA and glycine. GABA is the main inhibitory neurotransmitter in the retina and acts through GABA(A), GABA(B) and GABA(C) receptors, hyperpolarizing bipolar and amacrine cells, and decreasing action potentials in the ganglion cells,[242] although GABA(B) receptor activation has also been shown to enhance excitatory signals.[243] Glycine released from AII amacrine cells inhibits OFF cone bipolar cell neurotransmission. [244]

Direct evidence that these classic neurotransmitters in the retina modulate refractive development is relatively sparse. Guoping *et al.* reported that the ratio of glutamate to GABA was upregulated in myopic guinea pig eyes,[245] suggesting that the ratio of excitatory and inhibitory neurotransmitters may be important for myopic eye growth. Several studies in animals and humans implicate defects in glutamate receptors with myopia.[95,240,246–248] However, since the glutamate receptors are so tightly coupled with ON and OFF pathway function it is difficult to determine if these associations are due to glutamate receptors or the loss of normal visual transmission through the retina.

Experiments with GABA(A), GABA(B), and GABA(C) agonists and antagonists in chicks identified complex eye growth effects, including myopia from a GABA(A) agonist in non-

goggled eyes and reduced form-deprivation myopia from a number of agents.[249] GABA(B) receptor antagonists inhibit form-deprivation myopia in guinea pigs.[250–252] In mice with lens induced myopia, GABA transporter 1 levels are elevated in myopia retina.[253] Studies on glycine and myopia are absent from the literature. Perhaps due to the ubiquitous nature of these neurotransmitters for inhibitory signals and the absence of methods to selectively isolate these critical neurotransmitters, the role of these potential signals has been difficult to elucidate.

Dopamine is an important retinal neuromodulator that regulates circadian rhythms,[254] different aspects of visual function,[255] retinal gap junctions for optimal retinal sensitivity under different light levels[217] and light adaptation. [79,256] Dopamine synthesis and release occurs in a subset of dopaminergic amacrine and interplexiform cells[257,258] and is stimulated by ON pathway visual transmission. [259–261] Tyrosine hydroxylase (TH), the rate-limiting enzyme for dopamine synthesis, and dopamine are found throughout the retina.[262] The dopaminergic amacrine cells synapse onto the AII amacrine cells and have reciprocal synapses back to the rod ON bipolar cell.[259] There is morphological evidence that a subtype of ON bipolar cell synapses onto dopaminergic amacrine cells.[263,264]

Dopamine is one of the few biochemical signals that has been implicated in form-deprivation myopia in both chick and mammalian models.[81,82,265–273] Form-deprivation causes a decrease in dopamine levels which appears to be due to a decrease in dopamine biosynthesis[81,274] and not due to a decrease in the number of dopaminergic amacrine cells. [275] In addition, dopamine and the dopamine receptor agonist, apomorphine, reduce the expected axial elongation of experimental myopia in a dose-dependent fashion in chicks, rabbits, macaques, guinea pigs (only in form deprivation, not in lens defocus) and mice (although lower doses in mice appear to have the optimal affect).[81,265,268,276–278] Reducing retinal dopamine in mice using pharmacology[270] or genetic mutations[271] produces myopic refractions under normal visual experience. Dopamine-mediated refractive changes appear to be due to activation of dopamine receptors since co-administration of dopamine D2 receptor antagonists abolish the effect of apomorphine in the chick,[276] and genetic inactivation of D2 receptors reduces form-deprivation myopia in mice.[269] Furthermore, D2-like receptor agonists (and selective D4 receptor agonists) reduce form deprivation in tree shrews.[273] However, the role of dopamine signaling in refractive development and myopia is complex, since the depletion of retinal dopamine did not alter the response to form-deprivation,[271] C57BL6 mice do not have a measureable decrease in retinal dopamine with form-deprivation,[279] and the dopamine D1 receptor may also be involved.[272] Further evidence of the complexity is demonstrated by studies in guinea pigs with spontaneously occurring myopia that suggest D1, and not D2 receptors are the mediators of the dopamine effects in slowing refractive eye growth.[280]

Our traditional view of two photoreceptor types with strict roles in scotopic and photopic conditions has been challenged by a number of findings, including the additional connections of rods to cones and rods to OFF bipolar cell connections[216] and rods functioning effectively under daylight conditions.[281] Likewise, viewing each neurotransmitter/neuromodulator as providing an isolated signal to retinal neurons for refractive eye growth is also likely simplistic. For instance, both GABA and dopamine are

released by retinal dopaminergic cells,[282] and interactions of dopamine and GABA may modulate the response to form-deprivation.[283] Additionally, both GABA and dopamine can be released in response to light or depolarization of ON-bipolar cells. Since these two neurotransmitters/neuromodulators are so tightly linked and dopamine regulates circadian rhythms, it is difficult to determine which may be involved in signaling refractive eye growth.

Peptides, growth factors, and refractive eye growth

Other molecules also provide signaling in the retina, including glucagon, nitric oxide, growth factors, and retinoic acid, and they may also modulate refractive eye growth. Some of these molecules have also been linked to circadian rhythms or other neuromodulators known to control photoentrainment.[284] For instance, vasoactive intestinal polypeptide (VIP) may signal eye growth, since blocking VIP in chicks reduced the development of form-deprivation myopia,[285] and retinal levels of VIP increase with lid suture in primates.[286] Increasing glucagon signaling via agonists or exogenous injections can inhibit form-deprivation in chicks.[287,288] Although in a mouse model of form-deprivation myopia, expression of glucagon-related peptides did not change.[289] Apolipoprotein A-1 may also act like a ‘stop’ signal for refractive eye growth,[290] possibly by binding to retinoic acid.[291]

Growth factors have also been implicated as potential signals for refractive eye growth. Basic fibroblast growth factor (FGF2) and transforming growth factor beta (TGF-beta) appear to work in opposing directions in chick form-deprivation myopia, with FGF2 reducing myopia and TGF-beta having no effect alone, but blocking the effect of FGF2.[292] Vitreal injections of FGF2 and insulin-like growth factor (IGF1) created excessive vitreous chamber growth and high myopia in chicks with normal visual input.[293] FGF2 may also act downstream of dopaminergic amacrine cells,[274] creating a signaling pathway for scleral growth. While FGF2 expression increased in myopic guinea pigs, a screen of Chinese individuals for single nucleotide polymorphisms in FGF2 and high myopia did not show any association,[294] potentially revealing differences between avian myopia, mammalian models, and human myopia. However, a recent study showed that TGF-beta and FGF2 gene expression is increased in scleral desmocytes in the guinea pig after lens-induced myopia.[295]

Pathway from retina to optical structures in the eye

Regardless of which retinal circuits need to be stimulated for normal refractive development, the signaling molecule or signaling cascade needs to travel through the retina, RPE, choroid, and to the sclera to alter eye size. Thus, reviewing the receptor locations of the various signaling candidates and/or their effects on scleral cells may provide further insights into refractive eye growth mechanisms, keeping in mind that some of these signaling molecules directly or indirectly modulate circadian rhythms. In addition, we review potential signaling on the cornea that may alter corneal curvature and produce large changes in refractive power, particularly in the mouse model of myopia.

GABA receptors have been localized in chick cornea and sclera. GABA(C) receptor gene expression is found in chick scleral fibroblasts and chondrocytes,[296] and GABA(A) and GABA(C) receptors are localized to corneal epithelium.[297] GABAergic agents have been

shown to alter DNA and glycosaminoglycan content of scleral fibroblast in culture.[298] Glutamate and/or its receptors have not been reported in the sclera, but mGluR6 transcripts are found in corneal endothelium.[299] Finally, dopamine acts by volume transmission in the retina which means that dopamine receptors are found on numerous retinal neurons as well as dopamine D2 and D5 receptors on the RPE.[88,300–302] While the localization of dopamine receptors in isolated posterior sclera has not been reported, dopamine D1 receptors have been detected in the uveo-sclera.[303] Additionally, dopamine receptors have been located on the corneal endothelial and epithelial cells.[304,305] Finally, growth factors may influence scleral and/or corneal growth. TGF-beta and FGF2 genes are present in the sclera.[295] TGF-beta acts to regulate growth of scleral fibroblasts.[306] IGF2 receptor regulates cell differentiation in the cornea.[307] Localization of these receptors to corneal, RPE, and sclera may underlie modulation of eye size/shape for refractive eye growth as shown by changes in gene expression in RPE after lens defocus of chicks[308] and tree shrews,[113] and by gene expression changes in sclera of tree shrews with myopia.[309,310]

Attenuated circadian signals in modern societies

For most vertebrates, environmental light is the most important *Zeitgeber* (German, for ‘time giver’) for synchronizing circadian activity. The 24-h light:dark cycle entrains almost all circadian rhythms in the body, including the eye, to environmental light. The technical evolution of artificial lighting has markedly affected how biological systems, both humans and other terrestrial animals, interact with light. The pronounced differences in spatial, temporal and spectral properties of artificial compared to natural lighting impact the environments of all developed societies.[311,312] Indoor lighting is less intense and color-shifted compared to daytime outdoor lighting, depending on the characteristics of the illumination source.[313,314] The intensity levels of typical indoor lighting measure 100–500 lux; that of outdoor lighting ranges from 1000 to over 100 000 lux, depending on atmospheric conditions.[315,316] Sleep timing and melatonin rhythms, for instance, vary between time spent in a natural outdoor environment (e.g., camping) and in habitual indoors that include artificial light during both day and night.[317]

The situation during night arguably is even more complex than that during the day. The term ‘skyglow’ refers to diffuse luminance of the night sky from artificial sources, excluding light from the moon, stars and other natural lighting. Individual artificial lights at night illuminate directly the surrounding area. Broad areas of artificial lighting, as occurring in cities, illuminate the sky; and back scattering from atmospheric components, such as clouds or dust, create skyglow. Skyglow, or light pollution, is a major component of ambient illumination at night. The intensity of skyglow varies over 10 000-fold, hundreds of times more variation in night illumination than before the introduction of artificial lighting, and the radiance and extent of artificial light on the Earth’s surface is increasing.[318] Because of reflections from clouds, skyglow that originates from ground lighting is actually greater on overcast than clear nights; further, the luminance can change very rapidly as the cloud cover shifts.[319] Besides gross intensity effects, modern artificial lighting distorts the gradual and symmetrical light–dark transitions at the beginning and end of night; and skyglow may be greater in the evening than just before dawn because of human habits in the use of ground lighting.[319] Many uncertainties and assumptions underlie efforts to estimate the distribution

and intensity of ambient light at night. One worldwide atlas from satellite data shows marked differences in light intensity at night, with urban areas and economically developed regions far more affected than rural areas,[320] both within and between countries. In addition to skyglow, artificial light exposures at night include increasing use of light emitting electronics, such as televisions, computers, and hand held devices, all of which have been shown to disrupt normal sleeping behavior in young children and adolescents,[321,322] and can contribute to disruption of biological rhythms.

Of pertinence and concern here, increasingly literature points towards many adverse effects of artificial lighting on human health. Light synchronizes the circadian clock and, hence, circadian rhythms, to the light:dark cycle occurring not just daily but even seasonally; distortions in the 'natural' light:dark cycle act as major environmental stress factors. [323,324] The commonly hypothesized mechanism for adverse health effects from artificial patterns of lighting is disruption of endogenous circadian rhythms. Besides effects on sleep and mood, circadian disruptions in contemporary societies now seem to contribute to specific diseases, including some cancers, obesity, diabetes, and certain neurological diseases.[170,323,325–327] Current research suggests that artificial light at night is a major factor for these circadian disruptions and increased disease risks.[324,328]

Could these circadian disruptions in modern societies also be contributing to the increasing prevalence of myopia? Though far from proven, this now seems a plausible hypothesis. The increasing myopia prevalence is a relatively modern phenomenon in developed and developing societies, occurring concurrently with the evolution of more efficient lighting over the past 200 years: from gas and early incandescent sources (carbon arc, lime, etc.) to more efficient incandescent vacuum bulbs and now to more advanced alternative light sources (fluorescence, LEDs, etc.). The retina is the main or exclusive light sensing organ across the vertebrate kingdom, providing the photic input to entrain the systemic circadian system and containing its own endogenous circadian clock. During daytime, the comparatively low intensity levels of indoor lighting have long been proposed as contributing to myopia development. [43–46] Based on the circadian hypothesis proposed here, the resulting reduced strength[329] of the circadian signal from low intensity daytime lighting could provide a mechanism for myopia. The human eyelid behaves chiefly as a red-pass filter, with transmission estimates in the red of some 5%–20%[330,331]; thus even during sleep, light can reach the retina particularly from red-enriched sources like incandescent or specialized lighting, thus also dampening a circadian signal by confounding the dark phase.

Besides intensity, the color of light is increasingly recognized as influencing both circadian rhythms and refractive development. From available data in animals, blue–yellow opponency can entrain the circadian clock in fish[332] and permits more dependable tracking of twilight progression in mice than intensity,[333] phenomena that are likely more complex than melanopsin activation alone. Besides an influence of chromatic cues on the emmetropization mechanism, [334] the refractive impact of extended rearing under restricted chromaticity varies by species, with red light inducing myopia in chicks[335] and guinea pigs, [336] but inducing or shifting refraction towards hyperopia in tree shrews[337] and Rhesus monkeys.[338] These results raise questions about how chromaticity modulates refraction, including (1) the retinal pathways through which melanopsin and ipRGCs might potentially

act to influence eye growth via blue light exposure (see report of violet light having protecting effects)[339]; (2) whether retinal cells expressing the circadian clock link to long wavelength cones to influence refraction; and (3) how the timing and intensity of chromatic stimuli govern eye growth. Resolving questions such as these will require future research.

Summary

Given the retina's central role in entraining circadian rhythms to the light:dark cycle,[67] as well as refractive development, a role for circadian retinal functions in regulating postnatal eye growth is conceivable and conforms to data reviewed here. For many decades, researchers have studied the influence of ambient lighting on refractive development in laboratory animals. In chick and monkeys, altering the daily light:dark cycle by varying the duration[135,266,340,341] and intensity[120,342–344] of light leads to significant changes in normal eye growth and in ocular responses to goggles and spectacle lenses. Diurnal and/or circadian changes in ocular dimensions seem linked to refractive development [138]; and retinal neurotransmitters involved in refractive development, such as dopamine and GABA, also modulate retinal circadian functions.[4,67,249] Finally, the anti-myopia effects of light exposure in both animals and children might be hinting towards a correction of some type of circadian disruption. In fact, sleep disturbances have now been identified in myopic children and adolescents, [128,129,345] and sleep disorders may imply an underlying circadian rhythm disturbance in myopic children.

A proposed pathway that incorporates the retinal clock and eye growth rhythms in the regulation of postnatal eye growth and refraction is shown in Figure 8.[346] This scheme suggests that retinal neurotransmitter responses to visual images interact reciprocally with the retinal circadian clock. Light and possibly other *Zeitgebers*, such as temperature and diet, synchronize the clock to the diurnal cycle, but also could desynchronize the clock if delivered in a non-physiologic manner. Presumably, the retinal clock regulates the diurnal or circadian rhythms in ocular growth and eye dimensions, which may comprise the mechanism through which the clock impacts the overall refractive development of the eye. This hypothetical framework conforms to the clinical and laboratory observations reviewed here; but much work is needed to identify the molecular components of this pathway in experimental animals and, ultimately, to learn if and how this framework might provide a means to favorably modify refractive development in children. Pathways independent of the circadian clock likely also modify refractive development, and how non-circadian mechanisms might interact with the retinal clock and growth rhythms requires future investigation.

Hypothesizing a role for circadian disruption as a myopia mechanism suggests approaches for developing novel, behaviorally based anti-myopia therapies. For example, circadian disruptions could result from either decreased amplitude or a phase shift of circadian rhythms, neither of which have been studied directly in relation to childhood refraction. Arguing against a mechanism involving a simple reduction in rhythm amplitude is the overall modest effect of outdoor exposures on protecting children against myopia. However, nighttime artificial lighting is now recognized as a major circadian disruptor for many non-ocular clinical conditions and diseases associated with altered rhythms. While previously

proposed as a potential risk factor for myopia,[174] nighttime lighting effects have been largely dismissed by researchers in this area because of disparate findings in subsequent research.[175–178] Efforts to reduce ambient nighttime lighting, however, might increase the efficacy of outdoor exposures because reducing the intensity of nighttime lighting may enhance the circadian signal and augment the effects from elevated daytime lighting, as from outdoor exposures.

If the myopia risk mechanism in contemporary societies instead derives from a phase-shift of circadian rhythms in children, defining the nature of this may shift may lead to an effective therapy. The classic phase response curve, the relationship of bright light exposures to shifts of rhythms, is a basis for treating jet lag. The least effective times for using light exposures to shift circadian phases occur in the middle of the light phase, the so-called deadzone.[347,348] Available anti-myopia studies typically increase outdoor exposures in the middle of the day, the time when any light-induced shift on biological rhythms would be expected to be minimal. Study of the timing of light exposures also could be a productive research direction for altering refractive development, but such investigations would be more efficiently and rationally designed after defining the nature of any circadian disorder in ametropic children, if it indeed occurs.

A very incomplete understanding the mechanistic basis of refractive disorders continues to hamper introduction of rational, effective therapies. This review brings together many recent findings suggesting that circadian biology may provide a direction that could move the field forward. How circadian rhythms or clock related genes might directly link to the regulation of eye growth is not known. Nonetheless, a circadian hypothesis could shift the research in refractive development from eye-specific and descriptive clinical hypotheses to an area of very active medical/biological investigation with rapidly advancing molecular and biochemical insights. The area of circadian biology, though, is quite complex. Hopefully, the ideas proposed here will stimulate novel research directions needed to understand the mechanisms underlying refractive errors.

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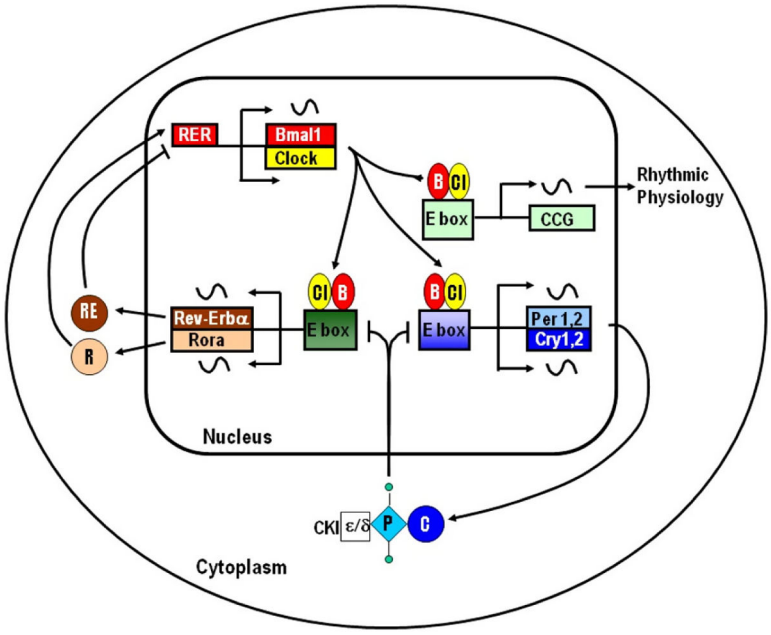

Figure 1.

Molecular mechanism of the circadian clock. Modified from Iuvone *et al.*,[58] with permission from Elsevier, Ltd.

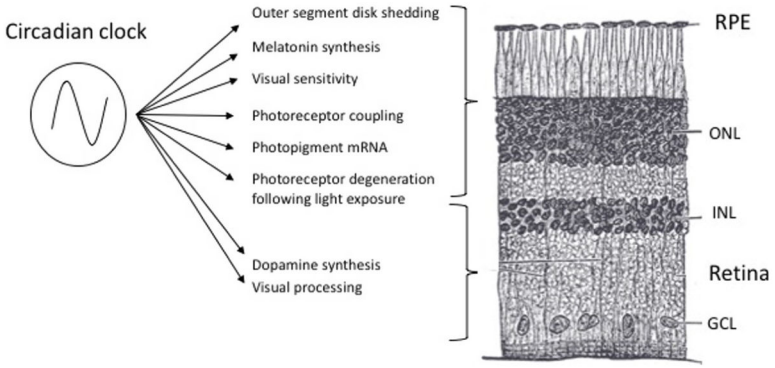

Figure 2.

Circadian processes in the retina and the retinal pigment epithelium, with their approximate location identified by retinal layer. RPE, retinal pigment epithelium; ONL, outer nuclear layer; INL, inner nuclear layer; GCL, ganglion cell layer. Modified from McMahon *et al.*,[67] with permission from Elsevier, Ltd.

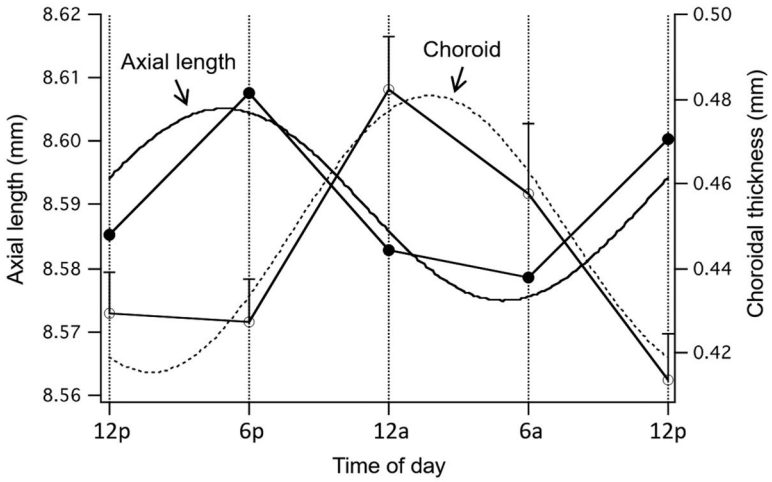

Figure 3.

Mean rhythms in axial length (black circles; left axis) and choroidal thickness (white circles; right axis) in normal chick eyes measured at 6 h intervals over 24 h. For axial length, the slope of the data for each eye (i.e., the underlying eye growth rate) was subtracted out to yield the 'cyclic component.' The curves are the sine waves with a fixed 24 h period fit to the data. From Nickla,[143] with permission from Springer.

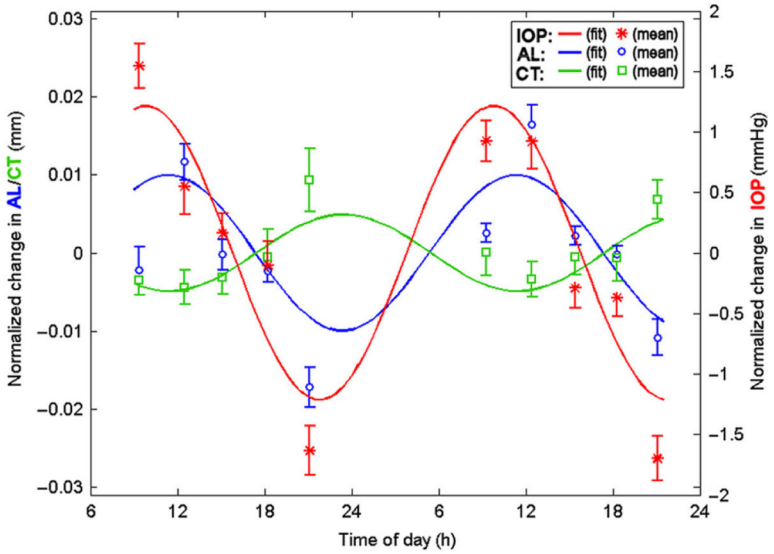

Figure 4.

Rhythms in axial length (AL, blue), choroidal thickness (CT, green) and intraocular pressure (IOP, red) in human subjects measured at 10 different times over 2 consecutive days (symbols), fit with fixed 24 h period sine waves. Note that the rhythms in axial length and choroidal thickness are in approximate anti-phase to one another. From Chakraborty, *et al.*, [148] with permission from Association for Research in Vision and Ophthalmology©.

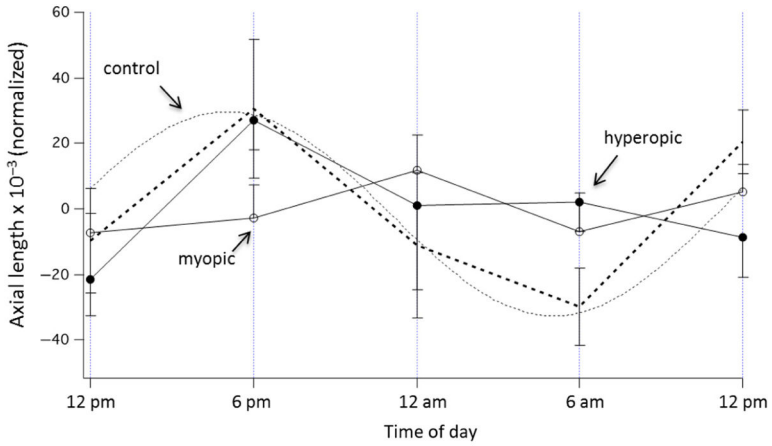

Figure 5.

Axial length (normalized to the mean) at 6 h intervals for chicks exposed to 2 h myopic (open symbols) or hyperopic (closed symbols) defocus in the morning (7 am–9 am), vs control eyes (dotted lines and sine wave fit). Note that data from both of the morning defocus conditions cannot be fit to a 24-h sine function (data from Nickla *et al.*).[153,162]

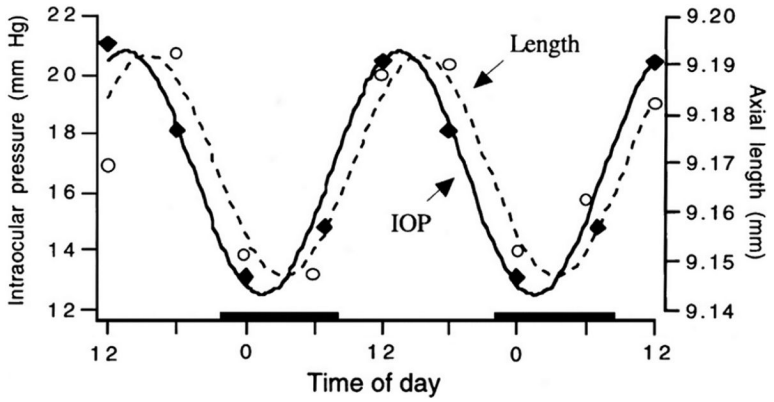

Figure 6.

The rhythms in IOP (black symbols) and axial length (open symbols), fit with fixed 24 h period sine waves. The data for the two parameters are from different sets of chicks ($n = 10$ in each group). Note that the rhythms in IOP are similar (almost in-phase) to the rhythms in axial length. Black bars indicate darkness. Nickla, *et al.*,[157] with permission from Academic Press Limited.

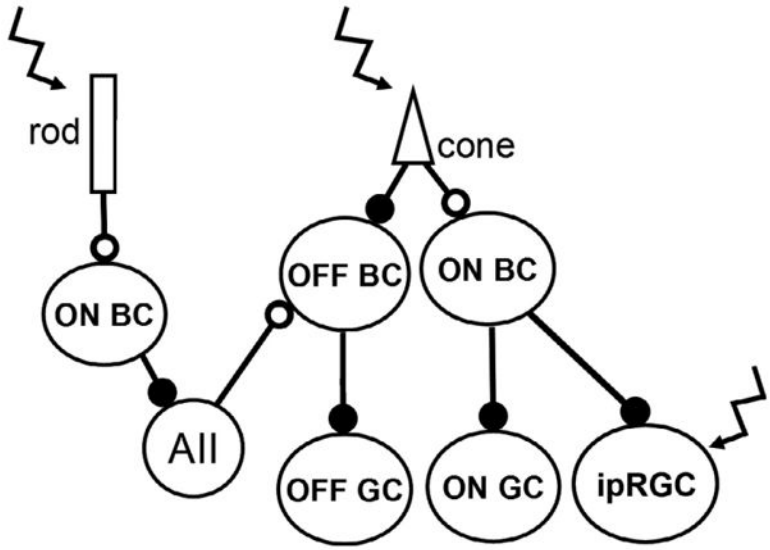

Figure 7.

Schematic of the ON and OFF pathway circuits in the mammalian retina. Open circles indicate sign-inverting synapses, closed circles indicate sign-conserving synapses, and zig-zag arrows indicate photosensitive cells. BC: bipolar cells; AII: type II amacrine cell, GC: ganglion cell; ipRGC: intrinsically photosensitive retinal ganglion cell. Modified from Soucy *et al.*, 1998.[216]

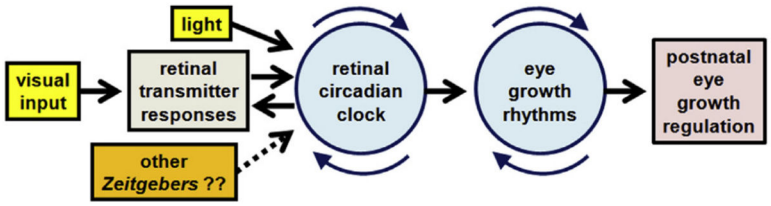

Figure 8.

A proposed pathway that incorporates the retinal clock and eye growth rhythms in the regulation of postnatal eye growth and refraction. Modified from Stone, *et al.*,[346] with permission from Elsevier.

Table 1

Summary of the results on refractive development with normal visual input for form-deprivation in genetic mouse mutants with dysfunctional photoreceptor or ON/OFF pathways

Elimination of	Effect on refractive development	Response to form-deprivation
Rod function[225]	Absent	Absent
Cone function[227]	Normal	Increased
ON pathway[239,240]	Normal or myopic	Increased
OFF pathway[241]	Normal	Normal