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Pharmacology of Myopia and Potential Role for Intrinsic Retinal Circadian Rhythms

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Abstract

Despite the high prevalence and public health impact of refractive errors, the mechanisms responsible for ametropias are poorly understood. Much evidence now supports the concept that the retina is central to the mechanism(s) regulating emmetropization and underlying refractive errors. Using a variety of pharmacologic methods and well-defined experimental eye growth models in laboratory animals, many retinal neurotransmitters and neuromodulators have been implicated in this process. Nonetheless, an accepted framework for understanding the molecular and/or cellular pathways that govern postnatal eye development is lacking. Here, we review two extensively studied signaling pathways whose general roles in refractive development are supported by both experimental and clinical data: acetylcholine signaling through muscarinic and/or nicotinic acetylcholine receptors and retinal dopamine pharmacology.

The muscarinic acetylcholine receptor antagonist atropine was first studied as an anti-myopia drug some two centuries ago, and much subsequent work has continued to connect muscarinic receptors to eye growth regulation. Recent research implicates a potential role of nicotinic acetylcholine receptors; and the refractive effects in population surveys of passive exposure to cigarette smoke, of which nicotine is a constituent, support clinical relevance. Reviewed here, many puzzling results inhibit formulating a mechanistic framework that explains acetylcholine's role in refractive development. How cholinergic receptor mechanisms might be used to develop acceptable approaches to normalize refractive development remains a challenge.

Retinal dopamine signaling not only has a putative role in refractive development, its upregulation by light comprises an important component of the retinal clock network and contributes to the regulation of retinal circadian physiology. During postnatal development, the ocular dimensions undergo circadian and/or diurnal fluctuations in magnitude; these rhythms shift in eyes developing experimental ametropia. Long-standing clinical ideas about myopia in particular have postulated a

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role for ambient lighting, although molecular or cellular mechanisms for these speculations have remained obscure. Experimental myopia induced by the wearing of a concave spectacle lens alters the retinal expression of a significant proportion of intrinsic circadian clock genes, as well as genes encoding a melatonin receptor and the photopigment melanopsin. Together this evidence suggests a hypothesis that the retinal clock and intrinsic retinal circadian rhythms may be fundamental to the mechanism(s) regulating refractive development, and that disruptions in circadian signals may produce refractive errors. Here we review the potential role of biological rhythms in refractive development. While much future research is needed, this hypothesis could unify many of the disparate clinical and laboratory observations addressing the pathogenesis of refractive errors.

Keywords

ametropia; acetylcholine; circadian rhythms; clock genes; dopamine; emmetropia; myopia; retina

1. Introduction

The mechanisms responsible for ametropias and for recent increases in myopia prevalence are unknown. Because of its high prevalence and public health impact, myopia is the form of ametropia that has received the most research attention. Long-held clinical ideas propose that myopia represents a “complex” disorder with both environmental and genetic causes (Farbrother et al., 2004; Hornbeak and Young, 2009; Klein et al., 2005; Morgan and Rose, 2005; Morgan et al., 2012; Zadnik, 1997). While genetic factors have been associated with both myopia and hyperopia and several chromosomal loci have been linked with human myopia (Hornbeak and Young, 2009; Wojciechowski, 2011; Wojciechowski et al., 2005), the literature is inconsistent; and the relative importance of genes vs. environment in myopia pathogenesis remains uncertain and controversial (Lyhne et al., 2001; Morgan and Rose, 2005; Rose et al., 2002). Despite population differences in prevalence levels (Pan et al., 2012), the rapid and pronounced increases in myopia prevalence (Pan et al., 2012; Rahi et al., 2011; Vitale et al., 2009) strongly support the hypothesis that major environmental influences are superimposed on, or may even act independently of, any genetic contribution to altered eye development (Morgan et al., 2012; Wojciechowski, 2011).

In the search for underlying pathogenetic mechanisms, research in laboratory animals has convincingly linked control of refraction to qualities of the visual image (Stone, 1997, 2008; Wallman, 1993; Wallman and Winawer, 2004). The laboratory findings have been extended to many species (e.g., chick, mouse, guinea pigs, tree shrew, various primates). The laboratory approaches most commonly use one of two models: 1) form-deprivation myopia, where blurring of the retinal image by an image diffusing goggle or eyelid suture accelerates ipsilateral eye growth and produces myopia; and 2) lens-induced ametropias, where shifting the image plane in front or behind the retina by spectacle lens wear produces compensating changes in eye growth that reposition the retina at the location of the shifted image position. Besides experimental animals, human children also develop form-deprivation myopia from obstructions in the visual axis that degrade the visual image, such as congenital ptosis or a scarred cornea (Meyer et al., 1999). In addition, lens-induced defocus or an accommodative stimulus cause transient adjustments of axial dimensions in the eyes of young human adults (Mallen et al., 2006; Read et al., 2010; Woodman et al., 2011), although data are not yet available on whether or not these transient adjustments influence human refractive development. Nevertheless, the visual mechanisms in these experimental models, or at least components of them, seem active in humans as well as animals (Kee et al., 2007; Smith et al., 2002). Given the many parallels in the mechanisms of refractive development now identified between chicks and mammals, including humans, the broad phylogenetic

conservation of the visual mechanisms governing refraction is truly remarkable (Stone, 2008; Wallman and Winawer, 2004), despite species differences in scleral and uveal structure.

As reviewed elsewhere (Norton, 1999; Stone, 1997, 2008; Stone and Khurana, 2010; Wallman and Nickla, 2010; Wallman and Winawer, 2004), much evidence now supports the notion that the visual mechanism(s) governing refractive development localize principally, though not necessarily exclusively, to the retina; and numerous retinal neurotransmitters or neuromodulators have now been implicated in refractive development. Despite this progress, there is no comprehensive, even hypothetical, framework to account for these diverse observations, and many questions remain. Because no direct neural pathways connect the sensory retina to either the choroid or sclera, even how retinal signals influence the overall growth of the eye remains speculative. One hypothesis is that the retinal pigment epithelium lies anatomically within the growth pathway and that the retinal pigment epithelium responds directly to retinal signals and/or transfers regulatory mediators between the retina and the choroid/sclera (Rymer and Wildsoet, 2005).

Detailed recent reviews of the application of contemporary pharmacology, emphasizing retinal mechanisms, are available (Ganesan and Wildsoet, 2010; Stone, 2008; Stone and Khurana, 2010). Here, we shall address selected evidence demonstrating that basic pharmacologic mechanisms uncovered in laboratory studies are relevant to refractive development in children, emphasizing cholinergic and dopaminergic pharmacology because much applicable data are available in children. Further, we shall discuss a hypothesis emerging from our own recent findings related to retinal dopamine mechanisms – namely, that endogenous retinal circadian rhythms may be fundamental to the mechanisms of emmetropization and that refractive errors might arise from disruptions of circadian control.

2. Cholinergic Mechanisms and Refractive Development

2.1 Muscarinic Acetylcholine Receptor Mechanisms

Muscarinic receptors are a group of G-protein coupled acetylcholine receptors, so-named because they historically were found to be activated by the fungal product muscarine. Five receptor subtypes are known in mammals that are designated m1-m5. Chicks, lacking a receptor homologous to the mammalian m1 receptor, express four muscarinic receptor subtypes corresponding to the other mammalian subtypes; the chick muscarinic receptor subtypes often are designated cm2-cm5 (Fischer et al., 1998a).

Clinicians have long hypothesized a central role for reading and other close-up activities in causing myopia, although this long-held belief is questioned by many contemporary findings (Dirani et al., 2009; Jones-Jordan et al., 2012; Jones et al., 2007; Mutti, 2010; Rose et al., 2008a; Rosenfield and Gilmartin, 1998). Under the assumption that accommodation links near vision tasks and ocular growth, the effect of the nonselective muscarinic antagonist atropine on myopia progression has been studied for two centuries (Wells, 1811). The vast literature on atropine as a therapeutic generally supports a favorable effect against myopia progression in children (Chua et al., 2006; Kennedy, 1995; Song et al., 2011) and against form-deprivation and lens-induced myopia in several experimental mammals (Ganesan and Wildsoet, 2010; Stone, 2008). Atropine's acute side effects of mydriasis and cycloplegia have hampered clinical acceptance of this drug despite its ostensible efficacy. Reducing the usual clinical concentrations of 0.5% or 1.0% in an effort to lessen these side effects has yielded variable amounts of partial anti-myopia effects in clinical studies (Chia et al., 2012; Shih et al., 1999). Several researchers have found that myopia progression resumes if atropine is stopped (Brodstein et al., 1984; Tong et al., 2009). Thus, despite extensive study, further investigations are warranted before recommending general clinical use of atropine.

Laboratory evidence suggests that the anti-myopia action of atropine is independent of the drug's inhibition of accommodation. For instance, the protective effect of atropine against experimental myopia in chick (McBrien et al., 1993b; Schmid and Wildsoet, 2004; Stone et al., 1991) contradicts the long-held view that atropine's anti-myopia activity results from inhibiting accommodation. Atropine has been long-known to be inactive at avian iris and ciliary muscles. In contrast to the smooth intraocular muscles of the mammalian eye, the avian intraocular muscles are striated muscles, and are activated by nicotinic rather than muscarinic acetylcholine receptors (Glasser and Howland, 1996). Indeed, cycloplegia in birds requires a neuromuscular blocking agent like curare. Muscarinic receptors of chicks are structured differently from those in mammals. Mammalian tissues express five distinct muscarinic acetylcholine receptor subtypes (Caulfield and Birdsall, 1998; Fischer et al., 1998a); the m3-muscarinic acetylcholine receptor mediates contraction of the iris and ciliary muscles in the mammal eye (Gil et al., 1997; Poyer et al., 1994). Atropine is a potent inhibitor with similar affinity to all five mammalian muscarinic receptor subtypes, and a number of antagonists with relative selectivity for the different muscarinic receptor subtypes have been evaluated in chick for anti-myopia activity. Of these, the antagonist pirenzepine has shown anti-myopia activity in chick, tree shrew and monkey (Cottrill and McBrien, 1996; Leech et al., 1995; Rickers and Schaeffel, 1995; Stone et al., 1991; Tigges et al., 1999). Only relatively selective, pirenzepine shows highest affinity in mammals for the m1 and also the m4 muscarinic receptor subtypes; but it also binds with lower affinities to the other subtypes (Caulfield and Birdsall, 1998).

Although birds lack a receptor homologous to the mammalian m1 receptor, pirenzepine binds with high affinity to the avian cm2 as well as to the cm4 muscarinic acetylcholine receptor subtypes (Jakubik and Tietje, 1994; Tietje and Nathanson, 1991). Consistent with the binding affinities for pirenzepine in mammalian and avian tissues, other data suggest a role for both m1 and m4 muscarinic receptor subtypes in inhibiting experimental myopia (Arumugam and McBrien, 2012; Cottrill et al., 2001b; McBrien et al., 2011). Regardless of the comparative roles of m1 vs. m4 cholinergic receptor subtypes, pirenzepine was long used in humans for gastrointestinal disease and, when tested topically in children, showed minimal effects on pupil size and accommodation (Bartlett et al., 2003), consistent with its comparatively low affinity for the m3 muscarinic acetylcholine receptor subtype (Caulfield and Birdsall, 1998). Accordingly, pirenzepine was studied in two multicenter clinical trials and found to reduce myopia progression in children by 40-50% (Siatkowski et al., 2004; Siatkowski et al., 2008; Tan et al., 2005). While supporting a presumptive role for muscarinic acetylcholine receptors in refractive development (see also section 2.4, below), the pirenzepine data also suggest that the muscarinic cholinergic pathway influencing myopia progression does not involve the m3 receptor mechanism. As another line of evidence, squirrels lack accommodation; but atropine inhibits the development of form-deprivation myopia in these animals (McBrien et al., 1993a). Hence, atropine's anti-myopia effect occurs independently of accommodation in both laboratory animals and in children.

2.2 Nicotinic Acetylcholine Receptor Mechanisms

The nicotinic acetylcholine receptors are a large and complex family of acetylcholine-gated non-selective cation channels, with multiple subunits. (Liu et al., 2009; Miwa et al., 2011; Wu and Lukas, 2011) Their name derives from the early observation that the plant alkaloid nicotine activates these receptors.

Several antagonists to the neural types of nicotinic acetylcholine receptors inhibit form deprivation myopia in chick (Stone et al., 2001), with nonselective antagonists in that study showing the greatest efficacy. Two of the antagonists enhanced the myopic growth response at low doses but inhibited it at higher doses, thus revealing multiphasic dose-response curves. These anti-myopia effects are consistent with action at neural acetylcholine receptors

based on the nature of the drugs, but the complexity of the dose-response curves precludes clear mechanistic interpretations. As examples, the complexities of the drug responses may follow actions at multiple receptor subtypes with dissimilar affinities, differential dose-related activation of specific receptor subtypes or involvement of multiple neuronal structures.

Nicotine is one of the prominent constituents of tobacco smoke. The suggestion that neural nicotinic acetylcholine receptors might influence refractive development in an experimental animal raised the question of whether exposure to tobacco smoke might influence refractive development of children. Several epidemiologic surveys subsequently have associated specific distributions of refraction with passive tobacco smoke exposure during childhood and even *in utero*. While the magnitude of the effect varied between studies, most investigations found reduced myopia prevalence and an overall refractive shift towards hyperopia in children passively exposed to environmental tobacco smoke, including exposure from maternal smoking during pregnancy (Borchert et al., 2011; El-Shazly, 2012; Ip et al., 2008; Saw et al., 2004; Stone et al., 2006). In addition to questionnaire data, one study included measurements of urinary cotinine, a metabolite of nicotine and a widely used biomarker for nicotine exposure; it found higher urinary cotinine levels in hyperopic than myopic/emmetropic children, and urinary cotinine levels correlated positively with increasing hyperopia (El-Shazly, 2012). One study with detailed pregnancy histories found that maternal smoking throughout pregnancy was not associated with myopia in the offspring, but that maternal smoking during just the first trimester was associated with high myopia (Rahi et al., 2011). Maternal smoking during pregnancy also has been associated with a higher risk of astigmatism in preschool children (McKean-Cowdin et al., 2011).

It is not possible at present to propose a specific mechanism to explain the action of tobacco smoke or nicotine on refractive development in children because of the many nicotinic acetylcholine receptor subtypes, the complexities of their signaling mechanisms, the uncertainty about potentially involved receptor subtypes with their different drug affinities, the unknown effects of activating receptors during development and the potential biological effects of other constituents of tobacco smoke. Despite these mechanistic uncertainties, the clinical studies suggest that passive exposure to tobacco smoke, as might occur from parental smoking, influences refractive development in children. Based on both the initial laboratory findings in experimental myopia and the subsequent epidemiological associations, a potential role of neural nicotinic acetylcholine receptors would seem to be a productive area for future mechanistically-based research.

2.3 Acetylcholinesterase Inhibition

About 50 years ago in Japan, an increasing incidence of myopia occurred in parallel with increasing use of organophosphate pesticides that act by inhibiting acetylcholinesterase and elevating acetylcholine levels (Dementi, 1994; Ishikawa S and Miyata, 1980). A variety of systemic alterations in autonomic and peripheral nervous function often accompanied the myopia, and the syndrome was termed “Saku disease” after a Japanese district with many affected subjects. Based on both epidemiology and laboratory investigations, this disorder was believed to result directly from organophosphate pesticide toxicity. In chicks, however, systemic or ocular administration of an acetylcholinesterase inhibitor did not alter the normal refractive development of eyes with intact visual input but instead inhibited form deprivation myopia (Cottrill et al., 2001a; Geller et al., 1998). It is not at present possible to reconcile the clinical and laboratory effects of this drug class on refractive development. Because these drugs increase acetylcholine levels that can act at either muscarinic or nicotinic acetylcholine receptors, it is also not possible to relate these results directly to the clinical and laboratory findings that muscarinic or nicotinic acetylcholine receptor antagonists exert anti-myopia effects. One acetylcholinesterase inhibitor increased retinal

levels of both acetylcholine and dopamine, and it was suggested that these drugs might affect experimental myopia indirectly by acting through retinal dopamine (Cottrill et al., 2001a), described below. As discussed elsewhere, however, local intra-retinal acetylcholine action, involvement of multiple acetylcholine receptors with different affinities or effects, or non-cholinergic drug effects might also provide the basis for these seemingly inconsistent findings.

2.4 The Cholinergic Conundrum

In addition to the conflicting results related to nicotinic acetylcholine receptor pharmacology and acetylcholinesterase inhibition already discussed, other puzzling results further hamper formulating a direct mechanistic explanation for the breadth of the clinical and laboratory findings supporting a cholinergic influence on refractive development.

The anatomical locus of a cholinergic mechanism regulating refraction is uncertain. Despite the general evidence implicating the retina in refractive control (Stone, 1997, 2008; Wallman, 1993; Wallman and Winawer, 2004) and the general developmental roles for cholinergic signaling (Abreu-Villaça et al., 2011), form deprivation does not alter retinal levels of acetylcholine, its biosynthetic enzyme choline acetyltransferase or choline (McBrien et al., 2001; Pendrak et al., 1995); and form deprivation also does not alter the number or affinity of cholinergic receptors in the retina (Vessey et al., 2002). These negative results, however, do not exclude retinal cholinergic involvement. Given the diversity of cholinergic cells and targets in the retina, it is possible that reciprocal changes develop in different retinal cells with no net measurable effect on total retinal content of acetylcholine/choline, enzyme activity or cholinergic receptor properties. Alternatively, there may be no perturbation in these parameters from form deprivation. When retinal cholinergic neurons are lesioned with toxins, emmetropization remains intact, form deprivation myopia continues to develop and the anti-myopia activity of atropine persists (Fischer et al., 1998b). These latter results suggest that cholinergic amacrine cells and muscarinic cholinergic receptors might not be essential for emmetropization or that a locus outside the neurosensory retina might account for cholinergic effects. However, the applied toxins incompletely lesioned the retinal cholinergic system (Fischer et al., 1998b); and any residual cholinergic network might be sufficient, e.g., if eye growth control operates through a low spatial resolution system. Further, the rapid effect of atropine on the retinal expression of the mRNA for the transcription factor *ZENK* in form-deprived chick eyes best conforms with a retinal, not an extra-retinal, site of action for the anti-myopia action of cholinergic drugs (Ashby et al., 2007).

In one study, there was marked variability in anti-myopia efficacy among a large series of muscarinic receptor antagonists injected into the vitreous cavity; some drugs showed partial or even no anti-myopia activity (Luft et al., 2003). The pertinent drug targets might lie outside the retina or even outside the eye, or perhaps undefined differences in drug penetration to the pertinent receptor(s) may account for the puzzling ineffectiveness of the inactive muscarinic antagonist drugs. Another possible explanation, as suggested by the authors, is that drug effects through non-muscarinic mechanisms may explain the limited anti-myopia action of some of the cholinergic antagonists (Luft et al., 2003). However, many of the drugs studied are not well characterized, particularly against chick muscarinic acetylcholine receptors, and some are well-known to bind to non-muscarinic receptors and may have opposing refractive effects to muscarinic antagonists; definitive explanations for these results are not now possible.

Identifying a candidate extra-retinal pathway to explain cholinergic effects has been difficult. Scleral cells in chick, for instance, do not express muscarinic cholinergic receptors by binding assay (Vessey et al., 2002). Consistent with this observation, muscarinic receptor

antagonists such as atropine alter proliferation and extracellular matrix production by scleral cells in culture (Lind et al., 1998); but the required doses are high and may not act via specific muscarinic receptor mechanisms. Ipsilateral to eyes with form deprivation myopia, choline acetyltransferase activity is suppressed in the ciliary ganglion and choroid (Pendrak et al., 1995), suggesting that cholinergic signaling already is reduced in these tissues. It is thus unclear why further reducing cholinergic activity with antagonist drugs acts to suppress myopia in chick. While accommodation is regulated through the ciliary ganglion, the long-held supposition that accommodation induces myopia is not supported by the contemporary research that casts doubt on a role for visual near work in myopia pathogenesis (see above). Reviewed elsewhere (Nickla and Wallman, 2010; Wallman and Nickla, 2010), the thickness of the choroid is modulated under visual and pharmacological conditions that influence eye growth, and investigating in greater detail cholinergic signaling in the choroid may be a productive future direction to understand the experimental and clinical roles of cholinergic signaling in refractive development.

Extensive clinical and laboratory research has repeatedly implicated cholinergic signaling in the mechanism governing refractive development. How or even whether acetylcholine modulates post-natal eye development at a molecular level and how cholinergic receptor mechanisms might be efficiently exploited to develop acceptable future therapies remains a challenge for clinical and basic investigators.

3. Retinal Dopamine, Light and Retinal Rhythms

3.1 Retinal dopamine and refractive development

One of the first non-cholinergic retinal neurotransmitter systems implicated in refractive development (Stone et al., 1989), the catecholamine dopamine is synthesized by a subset of retinal amacrine/interplexiform cells. Retinal dopamine normally oscillates in a diurnal pattern with storage levels and release rates higher during daytime than nighttime. Dopamine synthesis and release are stimulated by light and modulated by circadian clocks and melatonin (Iuvone et al., 2005; Tosini et al., 2008; Witkovsky, 2004). Reviewed elsewhere in greater detail (Ganesan and Wildsoet, 2010; Stone, 2008), fluctuations in dopamine metabolism accompany conditions modulating eye growth. The wearing of an image diffusing goggle or negative spectacle lens, both of which stimulate eye growth and induce myopia, reduces the daytime increase in dopamine metabolism; the wearing of positive spectacle lens, that inhibits eye growth and causes hyperopia, has the opposite effect on retinal dopamine (Guo et al., 1995; Iuvone et al., 1989; Iuvone et al., 1991; Stone et al., 1989). Ocular administration of dopamine agonists inhibits myopia from goggle or lens wear and also augments the hyperopic response from positive lens wear (Iuvone et al., 1991; Schmid and Wildsoet, 2004; Stone et al., 1989). The D₂ subtype dopamine receptor seems to mediate the inhibitory effect on form deprivation myopia (Rohrer et al., 1993). Brief periods of unobstructed vision prevent form deprivation myopia, an effect that can be blocked by antagonists of D₂-like dopamine receptors (McCarthy et al., 2007). These and other findings support the hypothesis that retinal dopaminergic amacrine cells lie in the pathway linking visual input to eye growth regulation (Ganesan and Wildsoet, 2010; Stone, 2008). Because of potential side effects outside the eye in children, dopaminergic drugs have not been investigated clinically as anti-myopia agents.

Like other tissues, the retina has an intrinsic clock mechanism to regulate its physiology to the daily cycle of light and dark. Discussed below and illustrated in Fig. 1, retinal dopamine is a component of the retinal clock network, exerting an opposing role to melatonin in regulating retinal physiology (Iuvone et al., 2005; Tosini et al., 2008). Dopamine has been implicated in retinal circadian rhythms of gene expression, protein phosphorylation, and

visual processing (Jackson et al., 2011; Jackson et al., 2012; Pozdeyev et al., 2008; Ruan et al., 2008).

In chick, a retinal “dark-light switch” model has been proposed that links the circadian rhythm of melatonin secretion by photoreceptors to the light phase by reciprocal activity of dopaminergic amacrine cells and a second amacrine cell type co-expressing enkephalin-, neurotensin- and somatostatin-like immunoreactivities, the so-called ENSLI amacrine cells (Morgan and Boelen, 1996). ENSLI amacrine cells have not been identified in other vertebrates, and it is not established whether functional equivalents exist in other species. Nonetheless, some data suggest potential roles for enkephalin and neurotensin in refractive development in chick. The light:dark cycling of leu-enkephalin is reduced in the retina of form-deprived chick eyes, and patterns of restored vision or strobe illumination that independently reduce the myopic response to form deprivation also at least partly re-establish the diurnal cycling of leu-enkephalin (McKenzie et al., 1997; Megaw et al., 1996). Similarly in chicks, strobe lighting re-establishes the cycling of retinal dopamine metabolism of form-deprived eyes (Rohrer et al., 1995), and dopaminergic receptors contribute to the action of brief periods of unimpaired vision to inhibit form-deprivation myopia (McCarthy et al., 2007). The nonspecific opiate antagonist naloxone blocks form-deprivation myopia in chicks, but the opiate agonist morphine has no effect. Of opiate drugs selective to one of the three opiate receptor subtypes, only kappa-selective drugs were active; but both an agonist and an antagonist inhibited form-deprivation myopia (Pickett Seltner et al., 1997). One report found increased expression of the mRNA for neurotensin in form-deprived chick eyes (McGlinn et al., 2007), but no other data are available on neurotensin and refractive development. Thus, the few available reports do not now provide conclusive evidence for a role of ENSLI amacrine cells in refractive development, but the possibility that they may interact with dopaminergic amacrine cells in regulating refractive development remains an intriguing possibility.

While it is not yet established whether the refractive role of dopaminergic amacrine cells, or perhaps their interaction with the ENSLI cells, relates to the retinal clock, evolving evidence suggests that there may be a connection. As perspective for the potential inter-relation of dopamine, the retinal clock and refraction, recent evidence for daily rhythms in ocular dimensions and the role of light exposure in refractive development will be summarized.

3.2 Diurnal rhythms of eye length and growth

In laboratory animals with non-restricted vision (Liu and Farid, 1998; Nickla et al., 2002; Nickla et al., 1998a, b; Papastergiou et al., 1998; Weiss and Schaeffel, 1993) and in humans (Brown et al., 2009; Mapstone and Clarke, 1985; Read et al., 2008; Stone et al., 2004; Wilson et al., 2006), the axial dimensions of the eye fluctuate in diurnal patterns. Ocular parameters that fluctuate include axial length, choroidal thickness, vitreous chamber depth and anterior chamber depth. Most studied in chick, these fluctuations in normally developing eyes result in eye growth principally during the daytime (Nickla et al., 1998b; Papastergiou et al., 1998; Weiss and Schaeffel, 1993). For chicks, these changes in ocular dimensions persist in constant dark, indicating that eye length fluctuations comprise a true circadian rhythm. (Campbell et al., 2012; Nickla et al., 2001) With form deprivation myopia, the overall growth is not only accelerated but the rhythms also become shifted so that daytime growth and nighttime growth are more equivalent (Nickla et al., 1998b; Papastergiou et al., 1998; Weiss and Schaeffel, 1993). Spectacle lens wear also shifts the fluctuations of these rhythms in chicks in patterns that suggest that eye growth rates may be affected by the phase relationship between diurnal axial length and choroidal thickness oscillations (Nickla, 2006). In children, no data at present exist on daily size fluctuations in eyes developing ametropias or whether these daily eye size fluctuations contribute to the mechanism(s) responsible for ametropias.

3.3 Ambient lighting and refractive development

The introduction of artificial lighting has dramatically altered the daily patterns of light exposure, especially in more developed regions of the world (Cinzano et al., 2001). There is growing concern that artificial lighting is now affecting human health (Navara and Nelson, 2007; Pauley, 2004) in such matters as cancer risk, endocrine function and metabolism (Anisimov, 2006; Bartness et al., 2012; Stevens and Rea, 2001; Wyse et al., 2011). Conforming in a general sense to this medical literature, ambient lighting influences refractive development in laboratory animals and seemingly in children. In fact, there is a long history of efforts to understand and relate light exposure to clinical refractive development (e.g., Brown and Carris, 1930; Cowan, 1942; Foulds and Luu, 2010; Rau, 1951; Zhilov, 1977). The available data on whether, or even if, modern patterns of lighting exposure impact eye development are contradictory and controversial; and a general framework to understand the interaction of light exposure with refractive development is needed.

Much studied in chick, altering the daily light:dark cycle influences the patterns of ocular growth. For example, rearing under constant light enlarges the chick eye while flattening the cornea (Jensen and Matson, 1957; Oishi and Murakami, 1985); hyperopia results because the marked corneal flattening reduces corneal power so much that the image plane is located behind the retina despite the elongated eye (Li et al., 1995; Stone et al., 1995). Constant light rearing of chicks modifies the ocular responses to goggle or spectacle lens wear (Bartmann et al., 1994; Guo et al., 1996; Padmanabhan et al., 2007; Stone et al., 1995). Rearing rhesus monkeys under constant light with or without a spectacle lens also affects refractive development, but the responses are much less pronounced in monkey than those in chick (Smith et al., 2001; Smith et al., 2003). For both chicks and monkeys, the constant light effects present a conceptual inconsistency: focused visual images at the retina should permit appropriate growth responses, but somehow altered lighting disrupts refractive development.

In mice, data on photoperiod effects on refraction are contradictory. Most investigators rear mice under a light:dark photoperiod to assess developmental phenomena (Pardue et al., 2008; Schaeffel, 2008, 2010). When reared under a light:dark period, increasing length of the light phase promotes axial myopia (Zhou et al., 2010). However, one group finds that mice emmetropize when reared under constant light and that they display more robust responses to goggles or minus lens wear under constant light than mice reared under a light:dark cycle (Tkatchenko et al., 2010). While more research is needed for a consensus on mice and the available data are difficult to interpret particularly because most mice species are nocturnal, refractive development in mice also seems influenced by photoperiod. The use of mice in myopia research is reviewed elsewhere in this issue.

For humans, photoperiod length also may influence refractive development. Some cross-sectional epidemiology surveys have found a higher myopia prevalence among children when darkness at night was disrupted by nighttime lighting during early childhood (Fig. 2) (Chapell et al., 2001; Czepita et al., 2004, 2005; Quinn et al., 1999); the initial report showed the strongest effect (Quinn et al., 1999). This result, however, has not been observed in other populations (Guggenheim et al., 2003; Gwiazda et al., 2000; Saw et al., 2001; Stone et al., 2006; Zadnik et al., 2000). Using the habitual times for sleeping/waking as a marker for light exposure, myopia in law students also was associated with less daily exposure to darkness (Loman et al., 2002). In the only available report to include ultrasound measurements of the eye, no refraction effect was found in the overall population; but nighttime ambient light exposure was associated both with more high myopia and with longer axial lengths (Saw et al., 2002). Even though results differ between studies, positive associations so far are in the same direction – interrupting the daily dark period with light is associated with myopia in children. Reconciling these disparate findings is speculative, but

they could relate to population differences or to the shortcomings of questionnaire-based epidemiology, such as reporting bias or unknown confounding variables.

More objective approaches to estimating influences of photoperiod length on human refractive development also suggest that light exposure may influence human refraction. Surveys of army conscripts in Finland, a country with marked variability in day length as well as light intensity throughout the year, found a higher prevalence of myopia in subjects from the country's far north (Vannas et al., 2003). Similarly, the geographic latitude of origin of human skulls demonstrates a positive correlation with orbital size, a presumed index of eye size (Pearce and Dunbar, 2012). These studies conform to a hypothesis that light exposure might affect eye development. Recent studies have now associated myopia with birth month (Fig. 3) (Deng and Gwiazda, 2011; Mandel et al., 2008; McMahon et al., 2009); this finding is consistent with an influence on refraction of perinatal day length or ambient light exposure in early infancy, although other physiologic effects on the infant or the pregnant mother are possible.

Besides photoperiod length, lighting intensity also influences eye development. In chicks, rearing under high intensity illumination modulates the effects of constant light (Cohen et al., 2008; Oishi and Murakami, 1985), inhibits the myopic response to diffuser wear (Ashby et al., 2009) and slows the compensation to minus spectacle lens wear (Fig. 4) (Ashby and Schaeffel, 2010). In monkeys, high ambient illumination also inhibits form-deprivation myopia (Smith et al., 2012). Rearing of chicks in low intensity light for several months lengthens the eye, elongates the vitreous chamber and induces myopia, relative to those effects in chicks reared under higher light levels (Fig. 5) (Cohen et al., 2011). Because decreasing light intensity reduces the rate of dopamine release in chick retina, retinal dopamine may comprise a link between daytime light intensity and refractive development in eyes with non-impaired visual input (Cohen et al., 2012).

Clinically, intriguing findings perhaps related to lighting intensity concern the relationship of refraction to outdoor activities during childhood. A long-standing observation (Cowan, 1942), modern clinical epidemiology has repeatedly confirmed associations of increased sports or outdoor activities during childhood or early adulthood with reduced myopia (Dirani et al., 2009; Jacobsen et al., 2008; Jones-Jordan et al., 2011; Jones et al., 2007; Mutti et al., 2002; Onal et al., 2007; Pärssinen and Lyyra, 1993; Rose et al., 2008a; Sherwin et al., 2012; Wu et al., 2010). Myopia progression also is slower during the summer than during the winter (Fulk et al., 2002), perhaps because children are outdoors for more time during the summer (Deng et al., 2010). Not all contemporary studies, however, substantiate this association between reduced myopia and increased outdoor activity (Lu et al., 2009; Saw et al., 2000; Zhang et al., 2010), including an assessment of myopia onset in children age 5 years and below (Low et al., 2010). The negative association of myopia and outdoor/sports activities now seems related to time spent outdoors rather than physical activity *per se* (Rose et al., 2008a). Children of Chinese ancestry in Singapore have a higher prevalence of myopia than children of Chinese ancestry living in Sydney, Australia; and the Singapore children spend less time in outdoor activities than those in Sydney (Rose et al., 2008b). Caucasian children living in Northern Ireland have a higher prevalence of ametropia than Caucasian children living in Sydney, Australia, a difference the authors suggest may relate to geographic differences in sunlight exposure and time spent in brighter outdoor light (French et al., 2012). Annual hours of sunshine also have been associated with blindness from malignant myopia, in patterns modified by subject age and gender (Daubs, 1982; Daubs, 1984). Besides intensity, however, indoor and outdoor environments and activities differ in other complex ways that might influence the visual system, such as different chromatic properties of the lighting or different image characteristics; and it has been suggested that systemic effects of outdoor lighting (e.g., on vitamin D metabolism) might

account for the apparent refractive effects of outdoor exposures (Mutti et al., 2012). Thus, a physiologic mechanism for these observations remains speculative. In the context of the effects of light intensity on eye development in laboratory animals, higher outdoor than indoor light intensity nonetheless is one hypothesized mechanism (Guggenheim et al., 2012; Rose et al., 2008a). Alternatively, an anti-myopia effect might follow improved image quality as a result of reduced pupil size in bright light. The influence of illumination intensity and/or the light:dark cycle on retinal dopamine release also has been proposed as a possible physiologic mechanism to explain the influence of light on refractive development, via the effects of retinal dopamine on eye growth. (Ashby et al., 2009; Ashby and Feldkaemper, 2010)

A conceptual dilemma, however, underlies much of the current thinking about light intensity and refractive development. Indoor rearing of laboratory animals, including chicks, tree shrews, marmosets and monkeys, with non-impaired visual input results in emmetropia and presumed “normal” refractive development (Bradley et al., 1999; Norton et al., 2003; Troilo and Judge, 1993; Wallman et al., 1981). Yet, the lower intensity of indoor vs. outdoor lighting is postulated as an environmental parameter promoting myopia in children. While bright light rearing inhibits form deprivation myopia in chicks and monkeys (Ashby et al., 2009; Smith et al., 2012), form deprivation *per se* is not the underlying cause of myopia in almost all affected children. More prolonged laboratory rearing periods than typically used in laboratory studies may be needed to demonstrate a refractive effect of indoor lighting (Cohen et al., 2011), or perhaps the mechanisms of experimental myopia in laboratory animals are not as closely related to the mechanisms underlying common childhood myopia as generally assumed. As other alternatives, the diverse observations about light on refraction may depend on lighting qualities besides just intensity; or the underlying biological mechanism of the refractive effects of lighting may be more complex than simply retinal dopamine release rates. Thus, how light influences refraction remains a conundrum, still not easily resolved.

3.4 Intrinsic retinal circadian rhythms

The retina has many endogenous circadian rhythms for signal transduction, neurochemical activity, gene transcription, metabolism, retinal structure and even gross retinal function (Golombek and Rosenstein, 2010; Storch et al., 2007). Entrainment is the process by which endogenous rhythms are synchronized to an environmental stimulus (the so-called “*Zeitgeber*,” from German for “time giver”) that influences circadian rhythm timing and maintains a stable phase relationship between biological rhythms and environmental stimuli. For most vertebrates, the dominant *Zeitgeber* is environmental light, but the influence of light on circadian rhythms is complex (Duffy and Czeisler, 2009; Johnson et al., 2003) and involves retinal dopamine (Jackson et al., 2011; Jackson et al., 2012; Yujnovsky et al., 2006). The light exposure patterns influencing refractive development (e.g., see above) often conform to the light exposure patterns used to study and model circadian rhythms.

Like other tissues with intrinsic circadian rhythms, the retina relies on a clock to match its rhythms to the 24 hour cycle of the day. Biological clocks are constructed of transcriptional and translational feedback loops consisting of the clock genes and their protein products (Tosini et al., 2008). Besides influencing its endogenous rhythms, an intact retinal clock even seems critical for processing visual input (Cameron et al., 2008; Storch et al., 2007).

3.4.1 Do circadian rhythms interface with refractive development?—Seeking to clarify the retina’s role in refractive development, several investigators have assessed retinal gene expression (i.e., mRNA expression) in eye growth models using microarrays (Ashby and Feldkaemper, 2010; McGlinn et al., 2007; Stone and Khurana, 2010; Stone et al., 2011;

Summers Rada and Wiechmann, 2009). As recently reviewed, proper interpretation of mRNA expression studies requires attention to methodologic details, including tissue preparation, gene profiling strategy, bioinformatics approach and subsequent validations; for a complex tissue like retina, expression profiles provide data pertinent to the tissue actually sampled (Stone and Khurana, 2010). Despite the caveats needed in interpreting these data, many potentially informative individual signaling molecules have emerged from these studies (Stone and Khurana, 2010).

Potentially related to dopamine's effects on refractive development, an intriguing set of differentially expressed retinal genes develops in chicks with myopia from minus lens wear (Stone et al., 2011). Lens-induced myopia alters the mRNA expression in the retina of a significant proportion of intrinsic clock genes, the gene to one of the receptors for melatonin (itself a major retinal output of the circadian clock), and a gene for melanopsin. Melanopsin is a light-sensitive pigment in non-photoreceptors of the vertebrate retina. In mammals, melanopsin is expressed by a subpopulation of intrinsically photosensitive retinal ganglion cells that project to brain centers controlling circadian rhythms and pupil size (Bailes and Lucas, 2010; Paul et al., 2009). In chick retina, melanopsin exists in two forms (Bellingham et al., 2006) and is expressed by horizontal and bipolar cells as well as ganglion cells (Tomonari et al., 2005). Dopaminergic amacrine cells express clock genes at comparatively high levels (Ruan et al., 2006). Significantly, melanopsin-containing ganglion cells also provide input to dopaminergic amacrine cells and influence their diurnal activity; and dopaminergic amacrine cells and melanopsin-containing retinal ganglion cells directly interact (Sakamoto et al., 2005; Viney et al., 2007; Vugler et al., 2007; Zhang et al., 2008). Moreover, melanopsin modulates diurnal rhythms of visual processing through the cone pathway in mouse retina (Barnard et al., 2006).

3.4.2 Refractive pharmacology and endogenous rhythms—In this context, the evidence that the diurnal variation in the biosynthetic and physiologic activity of dopaminergic amacrine cells modulates refractive development in both experimental mammals and birds (Iuvone et al., 1989; Iuvone et al., 1991; Stone, 2008; Stone et al., 1989) raises the possibility that endogenous rhythms may provide the link between image clarity, retinal pharmacology and refractive development. The expression of clock genes in dopaminergic amacrine cells and their interaction with melanopsin ganglion cells, just discussed, supports this hypothesis for future research. As indirect but further support for this hypothesis, other retinal neurotransmitters/neuromodulators implicated in refractive development (e.g., acetylcholine, GABA and VIP) (Chebib et al., 2009; Pickett Seltner and Stell, 1995; Stone, 2008; Stone et al., 1988; Stone et al., 2003; Tkatchenko et al., 2006) are already known to influence circadian rhythms in retina (Golombek and Rosenstein, 2010; Ruan et al., 2008; Steenhard and Besharse, 2000; Yujnovsky et al., 2006) or, if not yet studied in the eye, are known to modulate circadian rhythms in brain (Golombek and Rosenstein, 2010; Hut and Van der Zee, 2011; Mohawk and Tokahashi, 2011; O'Hara et al., 1998; Welsh et al., 2010).

Additional lines of evidence in chick also have suggested a potential role for circadian rhythms in refractive development. A short period of daily darkness inhibits the constant light response, hinting toward a circadian explanation for the effect (Li et al., 2000). Interrupting the dark period with three intermittent 5-minute light exposures/hour reduced the response to minus lens wear and inhibited contralateral eyes with intact visual input, and strobe lighting just before the onset and just after offset of light inhibited form-deprivation myopia; the authors speculated that their results are consistent with an influence of circadian rhythms on refractive development (Kee et al., 2001). Also, rearing chicks under continuous light but reducing the light intensity during “subjective” night inhibits this refractive response to constant light rearing, even when alternating between light levels that when held

constant induce the constant light response (Liu et al., 2004). The action of continuous light that oscillates in intensity within a 24 hour day to inhibit the response to rearing under constant intensity light also could be consistent with a circadian signal.

4. A hypothesis for emmetropization

Increasingly, studies suggest that endogenous retinal rhythms might interface with the mechanism(s) governing refractive development. These findings include the influence of dopamine rhythms on refractive development and endogenous retinal rhythms, the discovery of circadian rhythms in eye size and eye growth, the altered growth rhythms now known at least for chicks developing myopia, the effects of defocus on shifting daily eye dimension rhythms in chick, the extensive literature describing light effects on refractive development in laboratory animals and children and the microarray data identifying dysregulated circadian-rhythm related retinal genes in lens-induced myopia. While the observations do not yet provide a coherent molecular explanation, the breadth of these data suggests the hypothesis that intact intrinsic retinal circadian rhythms are fundamental to the mechanisms controlling refractive development and that refractive errors might arise from disruptions of circadian control (Fig. 6).

Establishing a central role for circadian retinal rhythms in refractive development could reconcile and unify many seemingly disparate observations. These include the increasing prevalence of myopia as societies become more economically advanced (perhaps from circadian disruptions due to increased artificial lighting), birth date effects (perhaps from influences of season on circadian rhythms of infants or pregnant mothers), the questions about indoor/outdoor activities with their varied lighting qualities, and the direct role of light itself. Circadian biology may also reconcile the seemingly contradictory observations that both less light (e.g., from indoor activities) and more light (e.g., from shorter or disrupted daily dark periods) are associated with more myopia in population surveys. Interrupting or altering the light:dark photoperiod has long been known to impact circadian rhythms (Golombek and Rosenstein, 2010); and dim lighting, including prior light exposures, can cause complex alternations of circadian physiology (Duffy and Czeisler, 2009; Turner and Mainster, 2008). Much future research is needed, though, to determine if and how circadian biology influences refractive development.

5. Conclusion

Using well-defined experimental eye growth models, the past several decades have seen increasing application of pharmacologic methods to learn the signaling mechanisms responsible for normal postnatal eye growth and for refractive errors. The literature on refractive development, laboratory and especially clinical, is vast; but understanding of the basic biological processes remains fragmentary, hypothetical, and often quite speculative. The large number of signaling molecules reported to be involved in this process also are not readily incorporated into a simplified eye growth model at present. Nonetheless, investigators are increasing applying basic pharmacology findings to the design of clinical investigations. Evolving clinical data now highlight several signaling pathways that might be central to normal and abnormal refractive development, and two promising pathways are reviewed here: acetylcholine signaling through muscarinic and/or nicotinic acetylcholine receptors and dopamine pharmacology. The extent to which the acetylcholine and dopamine/circadian pathways are distinct or interacting in modulating refractive development requires future study. Because designing clinical trials of drugs acceptable to patients and regulatory agencies has proved problematic (Stone, 2008), the influences of dopamine signaling may be providing an important lead. Based on the complex roles of retinal dopamine signaling on intrinsic retinal rhythms, future research on refraction, ocular

rhythms and endogenous circadian retinal rhythms may provide means to modulate refractive development through controlled light exposure rather than through drugs or optical manipulations.

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Highlights

- Complex, incompletely understood retinal functions influence postnatal eye growth.
- Both muscarinic and nicotinic mechanisms seem to affect refractive development.
- Retinal dopamine signaling and light exposures influence refractive development.
- Daily rhythms of eye dimensions may be linked with eye growth and refraction.
- Intrinsic retinal rhythms and clock genes may be fundamental to refractive control.

Fig. 1.

Dopamine, melatonin and retinal physiology. Dopamine and melatonin play opposing roles in retinal physiology. Both are diffusible neuromodulators, but dopamine promotes light adaptive retinal physiology and melatonin has dark-adaptive effects. The synthesis and release of dopamine and melatonin are modulated by circadian clocks, with dopamine released during the daytime and melatonin released at night. Light stimulates dopamine release and inhibits melatonin secretion. Both neuromodulators act on G protein-coupled receptors that are widely distributed in the retina. Melatonin inhibits dopamine release from amacrine/interplexiform cells and dopamine inhibits the release of melatonin from photoreceptor cells. Thus, the dopamine-secreting inner retinal neurons and melatonin-secreting photoreceptor cells form an intercellular feedback loop that regulates circadian retinal physiology. The dopamine neurons also interact with intrinsically photosensitive melanopsin-containing ganglion cells, providing another link to circadian physiology. Adapted from (Tosini et al., 2008) © 2008 Wiley Periodicals, Inc.

Fig. 2.

Influence of nighttime lighting before age 2 years on subsequent refraction. A history of increased nighttime light exposure during the first two years of life was associated with increased prevalence of myopia and reduced prevalence of emmetropia later in childhood ($P < 0.00001$). Hyperopia prevalence was unaffected. Despite the high statistical significance of these findings, the positive results in subsequent studies have been less strong; and they have not been replicated in other studies, as discussed in the text. Modified from (Quinn et al., 1999).

Fig. 3.

Myopia prevalence and birth month. The prevalence of moderate and severe myopia increased with increasing hours of daylight during the subjects' birth month among over 275,000 Israeli army conscripts. The solid line shows the averaged daily period of daylight for each month. From (Mandel et al., 2008) with permission from Elsevier.

Fig. 4.

The influence of light intensity on the refractive response to spectacle lens wear. Illustrating an effect of light intensity on emmetropization in the chick, the rate of refractive compensation of chicks wearing either a unilateral -7 diopter spectacle lens (in A) or a unilateral $+7$ diopter spectacle lens (in B) was altered by ambient daytime light intensity during a 12 hour light:dark cycle. Compared to chicks reared under 500 lux lighting (usual laboratory conditions), chicks that were exposed to 5 hours of intense 15,000 lux lighting in the middle of the day demonstrated a slowed response to minus lens wear (in A) and an accelerated response to plus lens wear (in B). The refractive development of the contralateral eyes with non-impaired visual input was not affected by light intensity in either group over this short rearing period. (Error bars: SEM; * $P < 0.05$; ** $P < 0.01$.) From (Ashby and Schaeffel, 2010); the Association for Research in Vision and Ophthalmology is the copyright holder.

Fig. 5.

The effect of light intensity on refractive development in normal chickens with non-impaired visual input. Chicks, reared from hatching under high (10,000 lux), medium (500 lux) or low (50 lux) illumination for 90 days, demonstrated different patterns of refractive development ($P < 0.0001$). At 90 days, the chicks reared under low intensity lighting were mildly myopic (-2.4 diopters), and those reared under high intensity lighting were slightly hyperopic ($+1.1$ D), with intermediate refractions for the cohort reared under medium intensity lighting. (Error bars: SD). Modified from (Cohen et al., 2011), with permission from Elsevier.

Fig. 6.

A hypothetical framework for the regulation of eye growth and refractive development. Proposed here is the possibility that intrinsic retinal circadian rhythms might be central to the signaling mechanism regulating refractive development. This scheme proposes that the neurotransmitter responses to visual input interact with the intrinsic retinal circadian clock. The clock also can be influenced by light and possibly other *Zeitgebers* (e.g., temperature, diet). The retinal clock presumably governs the daily rhythms in eye growth and ocular dimensions and thus could modulate the overall refractive development of the eye. While consistent with the diverse clinical and laboratory data discussed in the text, much work is needed to confirm the components of this hypothetical pathway. While not necessarily required, parallel but independent pathways might also contribute to the emmetropization process.