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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 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.

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

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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., 1993; 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