Long-wavelength (red) light produces hyperopia in juvenile and adolescent tree shrews

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ABSTRACT

In infant tree shrews, exposure to narrow-band long-wavelength (red) light, that stimulates long-wavelength sensitive cones almost exclusively, slows axial elongation and produces hyperopia. We asked if red light produces hyperopia in juvenile and adolescent animals, ages when plus lenses are ineffective. Animals were raised in fluorescent colony lighting (100–300 lux) until they began 13 days of red-light treatment at 11 (n = 5, "infant"), 35 (n = 5, "juvenile") or 95 (n = 5, "adolescent") days of visual experience (DVE). LEDs provided 527–749 lux on the cage floor. To control for the higher red illuminance, a fluorescent control group (n = 5) of juvenile (35 DVE) animals was exposed to ~975 lux. Refractions were measured daily; ocular component dimensions at the start and end of treatment and end of recovery in colony lighting. These groups were compared with normals (n = 7). In red light, the refractive state of both juvenile and adolescent animals became significantly (P < 0.05) hyperopic: juvenile 3.9 ± 1.0 diopters (D, mean ± SEM) vs. normal 0.8 ± 0.1 D; adolescent 1.6 ± 0.2 D vs. normal 0.4 ± 0.1 D. The fluorescent control group refractions (0.6 ± 0.3 D) were normal. In red-treated juveniles the vitreous chamber was significantly smaller than normal (P < 0.05): juvenile 2.67 ± 0.03 mm vs. normal 2.75 ± 0.02 mm. The choroid was also significantly thicker: juvenile 77 ± 4 µm vs. normal 57 ± 3 µm (P < 0.05). Although plus lenses do not restrain eye growth in juvenile tree shrews, the red light-induced slowed growth and hyperopia in juvenile and adolescent tree shrews demonstrates that the emmetropization mechanism is still capable of restraining eye growth at these ages.

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1. Introduction

As noted in many recent articles, there is a myopia epidemic in the U.S. and around the globe. Myopia in U.S. adults has increased from around 25% in the 1970′s to over 40% in 2004 (Dolgin, 2015; Lin, Chen, Hung, & Ko, 1988; Quek et al., 2004; Sperduto, Seigel, Roberts, & Rowland, 1983; Sun et al., 2012; Vitale, Sperduto, & Ferris, 2009). Myopia, especially higher levels, produces an elevated risk for retinal tears and detachment, choroidal degeneration, glaucoma, and cataract, making myopia a significant cause of blindness in the U.S. (Burton, 1989; Jones et al., 2007; Saw, Gazzard, Shih-Yen, & Chua, 2005; Vongphanit, Mitchell, & Wang, 2002; Zadnik, 2001). Thus, the rising prevalence of myopia presents a serious public health issue now and in the years to come. As myopia prevalence rises and myopes age, myopia-related blindness will also rise (Holden et al., 2015) unless we can devise ways

to block, or at least reduce, myopia development in children. Most studies in animal models have examined the emmetropization mechanism in the early postnatal stage (Zadnik & Mutti, 1995). More information is needed on how this mechanism functions at older ages, similar to those when children develop myopia.

Most young animals and human infants are born with eyes that have large refractive errors – tree shrews (Norton & McBrien, 1992), guinea pigs (Cook & Glasscock, 1951), marmosets (Graham & Judge, 1999), rhesus monkeys (Bradley, Fernandes, Lynn, Tigges, & Boothe, 1999), chicks (Pickett-Seltner, Sivak, & Pasternak, 1988), and humans (Chen et al., 2011; Cook & Glasscock, 1951), are generally hyperopic, although kestrels (Andison, Sivak, & Bird, 1992) are initially myopic. With age, the axial length (primarily, vitreous chamber depth) is rapidly adjusted to match the power of the eye's optics, achieving a state of *emmetropia* where the retina is located approximately at the focal plane (typically, a slight hyperopia remains that can be easily compensated for with accommodation, see Bradley et al., 1999; Norton & McBrien, 1992; Pickett-Seltner et al., 1988; Stenstrom, 1948). The dimensional precision required to achieve emmetropia is very high: for an adult human eye a change in axial length of just

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0.33 mm (out of a total axial length of about 24 mm) can result in a change in refraction of a diopter (Atchison et al., 2004).

It is now well established that an active emmetropization mechanism in the postnatal eye uses optical cues to dynamically adjust the eye's elongation rate to match the retinal location to that eye's focal plane (Mutti et al., 2005; Norton, 1999; Schaeffel & Howland, 1991; Smith et al., 2010a; Wildsoet, 1997). By fine-tuning the refractive state, the emmetropization mechanism achieves *and maintains* approximate emmetropia throughout the postnatal period (Amedo & Norton, 2012; Norton, 1999; Norton, Amedo, & Siegwart, 2010; Schaeffel & Feldkaemper, 2015; Smith, Hung, & Arumugam, 2014; Wallman & Winawer, 2004; Wildsoet, 1997).

In early postnatal development, the emmetropization mechanism responds appropriately to the sign of the refractive error. Induced hyperopia (focal plane behind the retina), either naturally occurring or induced by placing a minus-power lens in front of the eye, produces an increase in the axial elongation rate which moves the retina outwards to the focal plane. This reduces the hyperopia so the eye becomes emmetropic while wearing the lens, (lens "compensation"). Induced myopia (focal plane in front of the retina), typically produced by placing a positive (plus-power) lens in front of the eye, produces slowed axial elongation if applied early in the postnatal period. The maturing optics at the front of the eye (which decrease in optical power with age) gradually move the focal plane back to the retina; the slowed axial elongation produces compensation for the plus lens so that the eye becomes emmetropic while wearing the lens and hyperopic with the lens removed (Howlett & McFadden, 2009; Hung, Crawford, & Smith, 1995; Irving, Sivak, & Callender, 1992; Metlapally & McBrien, 2008; Mutti et al., 2005; Norton et al., 2010; Schaeffel, Glasser, & Howland, 1988; Shen & Sivak, 2007; Smith & Hung, 1999; Troilo, Totonelly, & Harb, 2009; Wallman & Winawer, 2004; Wildsoet, 1997).

After achieving a near-emmetropic refractive state during infantile postnatal development, the emmetropization mechanism remains active through the juvenile and adolescent stages, maintaining emmetropia even though the axial length of the eyes continues to increase. During these older ages, many animals continue to show a robust response to the increased hyperopia produced by starting to wear a minus lens, or to the lack of images produced by wearing a translucent diffuser ("form deprivation," which like minus lenses, also induces myopia) (Norton & Rada, 1995; Papastergiou et al., 1998; Smith, Bradley, Fernandes, & Boothe, 1999; Troilo, Nickla, & Wildsoet, 2000). However, in tree shrews, the ability of the emmetropization mechanism to compensate for a plus lens declines rapidly with age. Unlike infantile tree shrews, juvenile tree shrews wearing plus lenses do not slow the elongation rate of the eye. Normal elongation continues and the eyes remain myopic with the lens in place Siegwart and Norton (2010).

Although refractive myopia can be created in an emmetropic eye by wearing a plus lens, it can also be created by removing a negative lens or diffuser after the eyes have elongated and compensated for the minus lens. Upon lens removal, the elongated eyes are myopic (measured with the lens or diffuser removed). In response, the elongation rate is slowed and refractions return to normal levels, ("recovery from induced myopia").

In contrast to the lack of compensation for plus lenses, juvenile and adolescent tree shrews recover robustly from an induced myopia (Norton et al., 2010). The continued recovery response in juvenile and adolescent animals with induced myopia demonstrates that the emmetropization mechanism can detect and respond to the myopic refractive state over an extended age range with this species (Norton et al., 2010; Wallman & Adams, 1987). Refractively, the myopia that occurs when a minus lens is removed after compensation is very similar to the myopia that is measured when

plus-lens wear begins in a normal eye. It is therefore a puzzle why plus lenses do not cause slowed axial elongation and refractive compensation at these older ages.

It has been suggested that an important difference between the lack of response to a plus lens in a normal eye vs. recovery from induced myopia is that eyes with induced myopia are elongated whereas a normal eye is not. Siegwart and Norton (2010) suggested that, in a normal-size eye, the emmetropization mechanism may not be able to slow axial elongation below a genetically pre-programmed minimum amount. In contrast, in an eye that has been elongated after minus lens wear, the sclera has undergone remodeling of the extracellular matrix and has altered protein and mRNA levels (Frost & Guo, 2012; Grytz & Siegwart, 2015; Guo, Frost, He, Siegwart, & Norton, 2013; Siegwart & Norton, 1999). The altered sclera may respond to the signals from the emmetropization mechanism although normal sclera cannot.

Although optical blur is likely a powerful visual cue used by the emmetropization system to guide eyes to emmetropia and to maintain emmetropia, it need not be the only one. The full range of visual cues that the emmetropization mechanism uses to determine the amount and sign of refractive error are still poorly understood. Longitudinal chromatic aberration (LCA) could potentially be used as a cue to determine the sign of refractive error because long wavelength ("red") light is focused farther from the cornea than is short wavelength ("blue") light. Most mammals are dichromats, with their retinas containing only short-wavelength sensitive (SWS) cones and longer-wavelength sensitive (LWS) cones. Indeed, it has been argued that dichromacy is the baseline of mammalian color vision (Jacobs, 1993). If a retinal image contains many wavelengths, and if the long (red) wavelengths are in focus but short (blue) wavelengths are out of focus, this could signal the emmetropization mechanism that the eye has become long enough, or too long, and the mechanism should slow the axial elongation rate. There is strong evidence that the emmetropization mechanism in chicks (which have four cone types) can make use of LCA cues (Britton, Hanowsky, & Rucker, 2014; Graef & Schaeffel, 2012; Rucker & Osorio, 2008; Rucker & Wallman, 2008, 2009, 2012).

In infant tree shrews (dichromatic mammals closely related to primates) (Luckett, 1980) we have recently found that narrow-band red light, that only stimulates the LWS cones, produces slowed axial elongation and prevents the normal decrease in refraction from hyperopia to emmetropia so that the eyes remain substantially hyperopic (Gawne, Siegwart, Ward, & Norton, 2017). Similar results have been found in infant monkeys (Smith et al., 2015). The robust hyperopia and slowed axial elongation produced by red light in infant tree shrews led us to ask if red light can slow axial elongation in older, juvenile and adolescent, tree shrews at ages when plus lens wear is ineffective.

2. Materials and methods

2.1. Subjects and experimental groups

The tree shrews used in this study were raised in the UAB Tree Shrew Core by their mothers until weaning. The colony is maintained on a 14-h light on/10 h light off cycle (Guo et al., 2013; He, Frost, Siegwart, & Norton, 2014; McBrien & Norton, 1992). Fluorescent lighting (F34CW RS WM ECO) provided illuminance of 100–300 lux on the floor of the cages. All procedures complied with the Association for Research in Vision and Ophthalmology (ARVO) statement for the use of animals in ophthalmic and visual research and were approved by the Institutional Animal Care and Use Committee of the University of Alabama at Birmingham (UAB).