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Incremental retinal-defocus theory of myopia development—Schematic analysis and computer simulation

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Abstract

Previous theories of myopia development involved subtle and complex processes such as the sensing and analyzing of chromatic aberration, spherical aberration, spatial gradient of blur, or spatial frequency content of the retinal image, but they have not been able to explain satisfactorily the diverse experimental results reported in the literature. On the other hand, our newly proposed incremental retinal-defocus theory (IRDT) has been able to explain all of these results. This theory is based on a relatively simple and direct mechanism for the regulation of ocular growth. It states that a time-averaged decrease in retinal-image defocus area decreases the rate of release of retinal neuromodulators, which decreases the rate of retinal proteoglycan synthesis with an associated decrease in scleral structural integrity. This increases the rate of scleral growth, and in turn the eye's axial length, which leads to myopia. Our schematic analysis has provided a clear explanation for the eye's ability to grow in the appropriate direction under a wide range of experimental conditions. In addition, the theory has been able to explain how repeated cycles of nearwork-induced transient myopia leads to repeated periods of decreased retinal-image defocus, whose cumulative effect over an extended period of time results in an increase in axial growth that leads to permanent myopia. Thus, this unifying theory forms the basis for understanding the underlying retinal and scleral mechanisms of myopia development.

Keywords: Myopia; Refraction; Retinal-defocus; Under-correction; Constant light; Nearwork-induced transient myopia; IRDT model; Computer simulation

1. Introduction

Myopia, or nearsightedness, is a worldwide public health concern [1]. It affects 25% of the adult population in the United States [2] and 75% or more of the adult population in Asian countries such as Taiwan [3]. It can be corrected by optical means, but the estimated annualized cost to consumers in the United States for vision examinations and corrective lenses is $4.6 billion [4]. Furthermore, the wearing of spectacles for myopia may restrict one's vocational and avocational options [5]. Surgical techniques to reduce myopia are available, but they are expensive [6] and are not covered by health insurance. Furthermore, despite the continual developments and technological improvements over the past 20 years, there are still surgical and post-surgical risks, along with possible side effects such as long-term hazy vision and dry eye [4]. Moreover, surgery does not prevent the subsequent development of adult-onset myopia or other age-related refractive changes [4]. For these reasons, the slowing of myopic progression, as well as the prevention of its initial occurrence, has been of considerable interest to clinicians, scientists, and public health officials alike for decades.

Under normal genetic development during infancy, there is an inherent mismatch between the optical power of the cornea/lens complex and the axial length of the eyeball [7]. Yet, as the normal eye matures, the cornea/lens and surrounding ocular tunics begin to develop in concert to provide a relatively precisely focused image on the retina [6,8]. This process is called emmetropization [9]. Certain critical information is used to coordinate the cornea/lens and axial growth. One of the most important cues for regulating axial growth is retinal-image defocus [10–13]. Cornea/lens growth and its consequent change in optical power alters the amount of defocus, but an appropriate

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change in the axial length growth rate acts to reduce this defocus, and in turn restore the balance between these two components. Since the basic growth of the cornea/lens is genetically predetermined [14–17], emmetropization only involves the regulation and modulation of axial length growth [10–13].

Emmetropization also occurs as a result of environmentally induced conditions. This is evident in numerous studies which have attempted to determine the effect of various optically based manipulations of retinal-image quality on induced ocular growth and overall refractive development. The findings have been mixed with respect to the resultant direction of refractive shift. Some manipulations produced a myopic shift. These included: graded diffusers [18], black occluder contact lenses [19,20], purposeful under-correction for myopia [21,22], and prolonged nearwork [6,23]. On the other hand, other manipulations resulted in a hyperopic shift. These included: very strong diffusers [24,25], crystalline lens removal [26], initial imposition of graded diffusers [18], and constant light exposure [27–30]. Furthermore, manipulations using plus or minus lenses in the chick [31], tree shrew [32,33], and monkey [34] have resulted in either hyperopic or myopic growth, respectively.

The mechanism for the short-term emmetropization process appeared to be relatively simple: visual feedback related to retinal-image defocus could provide the requisite cortical control signal to regulate both the direction and magnitude of axial growth. However, such appropriate changes in growth rate occurred even when the optic nerve was severed [35,36] or the midbrain nuclei for controlling accommodation were lesioned [37], thereby precluding any central or cortically based visual feedback mechanism. *Thus*, *the retina is the site for controlling the rate of axial length growth.* Moreover, since defocus blur per se is an even-error signal [38], it lacks the requisite directional sensitivity for controlling axial growth. For these reasons, the controlling mechanism for the short-term emmetropization process, and in turn the long-term development of myopia, has remained elusive and puzzling to both researchers and clinicians alike for decades.

2. Mechanisms for control of ocular growth

2.1. Previously proposed mechanisms

Other mechanisms have been proposed for determining the attributes of blur that are critical for controlling axial growth. These involve rather complicated processes such as sensing and analyzing chromatic aberration, spherical aberration, spatial gradient of blur, or its spatial frequency content [39,40]. However, they have not been able to explain satisfactorily the regulation of ocular growth. A more recently proposed mechanism involves contrast adaptation [41–43]. Heinrich and Bach [43] found that contrast adaptation occurred for high but not low spatial frequencies in humans. They speculated that this may be a mechanism for discerning between a low contrast stimulus and retinal-image defocus, and in turn emmetropization control. And, Diether et al. [41] found an approximate relationship between change in contrast adaptation and change in refraction after wearing occluders in chickens. However, they did not find a significant difference in contrast adaptation after wearing plus or minus lenses. Moreover, the threshold for significant contrast adaptation effects with intact accommodation was about 4 D of defocus, thus precluding its sensitivity to lower dioptric values of retinal-image defocus. Thus, these results on contrast adaptation effects have been mixed.

In addition, it has been found that choroidal thickness changes occur in the same direction as the related axial length changes [12,13]. Hence, Wallman [12,13] speculated that the choroid might play a major role in myopia development [44,45] rather than only a small to negligible role as suggested by our theory. The resolution of the dilemma is as follows: although a relationship between changes in retinal-image defocus and choroidal thickness has been noted, the *amount of thickness change was too small* to account for most of the refractive change found [44,46]. Instead, the relationship is more likely the result of neuromodulators, or a cascade of neurochemicals related to the release of the neuromodulators [12,13,47–49], passing through the choroid to reach the sclera. Transit of these neuromodulators through the vascular choroid may result, as in the case of the monkey, in a volume change that is observed as a correlated change in choroidal thickness [44,45,50]. However, this change in choroidal thickness would have relatively little direct effect on axial elongation, but rather would provide the medium for the signal cascade from the retina to the sclera as proposed in both our theory as well as that of Wallman [12,13].

2.2. Basic principles of IRDT

In contrast to these other theories, our unifying theory of refractive error development has been able to account for all known clinical and laboratory experimental results [51–58].

Two fundamental insights underlie the incremental retinal-defocus theory (IRDT), which for simplicity is herein called "our theory". First, the presence of retinal-image defocus has been shown to be critical in the development of environmentally induced refractive error [31–34]. Yet, retinal-defocus area (i.e., size of the retinal blur circle, corresponding to a point light source) is an even-error signal, which provides magnitude but not directional information (i.e., over-focused and under-focused retinal images of equal size would be optically indistinguishable). Hence, retinal-defocus area information alone is insufficient to produce refractive error in a consistent direction (i.e., either myopia or hyperopia). Second, manipulation of the visual environment is effective in producing and/or modulating refractive error development, mainly during the ocular growth and maturational period up to the mid-teens [59], although this may occur even in early adulthood under extreme-near visual conditions [60]. This demonstrates the importance of a time-dependent element in producing refractive error. However, environmental manipulations over a given time period have been found to be ineffective in mature adults [59]. Hence, the time-dependent factor must also be accompanied by a time window of susceptibility.

Although, each insight alone is insufficient for a complete theory, when these two insights are combined, they provide