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Differential retinal-defocus magnitude during eye growth provides the appropriate direction signal

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SUMMARY

Introduction: The rate of ocular growth can be modified by the imposition of either plus or minus lenses before the eyes, which creates changes in retinal defocus. Several hypotheses with relatively complicated mechanisms have been proposed to explain these changes, but the underlying mechanism has remained elusive.
Material and methods: Our new analysis using schematic models, however, provides a relatively simple and logically-consistent explanation of how retinal defocus magnitude alone during ocular growth gives the requisite sign for an appropriate change in ocular growth rate.
Results: During a normal genetically-determined incremental increase in axial length, the presence of either an imposed plus or minus lens results in an increase or decrease, respectively, of the blur circle magnitude. Neuromodulators in the retina are proposed to regulate the sensitivity to retinal-image contrast by means of a local feedback mechanism, and the alteration in retinal-image contrast associated with the change in blur circle causes an increase or decrease, respectively, in the rate of release of neuromodulators as well as the rate of proteoglycan synthesis, the latter being associated with the structural integrity of the sclera.
Conclusion: This provides the critical sign, as well as amplitude, information needed to modulate appropriately the rate of eye growth, to result in a decrease or increase, respectively, in the rate of ocular growth.

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INTRODUCTION

If the cornea/lens and the ocular tunic grow in concert, the optical power and the axial length are perfectly matched to provide a precisely focused image on the retina. However, if the axial length grows more rapidly than the corresponding cornea/lens power, this mismatch results in myopia. Both genetic and environmental factors play important roles in refractive error development [1–4]. An important environmental factor is chronic exposure to retinal defocus.

However, one of the long-standing puzzles in the research on refractive error development has been how the eye distinguishes the direction of growth based on the blur information alone, since blur is an even-error signal, and thus it should be insensitive with respect to direction or sign [1,5]. Yet, it has been shown in research in the chick [6], tree shrew [7,8], and monkey [9] that the eye becomes more hyperopic or myopic with the imposition of relatively large magnitudes of plus or minus lenses, respectively. This refractive shift, called emmetropization, is highly correlated with changes in axial length [6–9]. Moreover, the stimulus for ocular growth occurs locally at the retinal level because this occurs even when the optic nerve is severed [10].

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A clue as to the how the ocular growth rate may be controlled by blur information alone became evident in a recent model of refractive error development proposed by us [11]. Simulation results indicated that refractive error and the absolute value of the accommodative error, or retinal defocus (which provides the perception of blur if the defocus is of sufficient magnitude), are involved in a long-term feedback loop in which they interact and modulate each other. This suggests that it is not the sign of the retinal error per se (which is plus for lag of accommodation, and minus for lead of accommodation), but rather a property related to the magnitude of the retinal defocus itself, that governs the appropriate rate of axial length growth relative to normal. We therefore examined in more detail how the change in magnitude of retinal defocus during an increment of genetically-determined axial length growth can provide the necessary information for directional modulation of growth rate.

MATERIAL AND METHODS

The development of a schematic analysis for the control of ocular growth rate requires the conceptual linking of a number of relatively complex topics including cornea and lens growth, optics of the eye, retinal neural signal processing, and scleral growth. The fundamental principles of the process for control of ocular growth rate may be understood in terms of answers to three critical questions: (1) What is the contribution of the cornea and lens to the emmetropization process? (2) How do retinal neurochemicals process the retinal-defocus information? and (3) How is this information used to regulate the rate of ocular growth under the conditions of large imposed plus and minus lens with relatively large defocus magnitudes, as well as prolonged nearwork with a relatively smaller defocus magnitude? The answers to these questions are presented in detail below. The figures were drawn using PowerPoint and Simulink.

RESULTS AND DISCUSSION

(1) Corneal growth is not part of emmetropization process after age 2 years

During the first two years of life, the cornea and axial length grow rapidly and in concert as part of the emmetropization process [12–14]. Afterwards, corneal power remains relatively stable [15–18] until the adult years, when it may increase slightly [17,19]. Since corneal flattening would be needed to balance the axial length growth, it is clear that the cornea plays little or no role in the emmetropization process after the first 2 years of life [15, 17,18]. Thus, during the school years, the major portion of emmetropization must be due to coordination of an axial length increase with a corresponding reduction in crystalline lens power [19]. However, since there is no evidence that visual feedback plays any role in the growth of the lens [15,20], emmetropization during this period to any large artificially-induced retinal-image defocus must be due only to changes of axial length growth.

In addition to its lack of contribution to emmetropization during this period, the cornea may even steepen during the childhood years [15], and along with axial length growth, actually contribute to myopia development [15,21]. Corneal steepening during this period would be opposite of that needed for emmetropization, and thus is unlikely to be controlled by visual feedback processes. Moreover, Goss and Jackson [18] found that after applying appropriate statistics to account for errors associated with multiple comparisons, their previously found weak relationship between myopia and increased corneal power was no longer statistically significant.

Further evidence for a lack of corneal involvement comes from animal studies. Studies on imposed-lens treatment in chicks revealed an absence of statistically significant effect on corneal growth [6,22,23]. Also, Schaeffel et al. [6] found that eyes that had worn plus lenses exhibited significantly shorter axial length than the eyes that had worn minus lenses, but that there was no significant difference in corneal curvature, anterior chamber depth, crystalline lens thickness, or calculated crystalline lens power. Moreover, in a deprivation study, Siegwart and Norton [23] found significant corneal flattening in the deprived eye of the tree shrew, which they attributed to the pressure on the eyelid during lid closure rather than the light deprivation itself.

(2) Neuromodulators control sensitivity to changes in retinal-image contrast

The retina contains a large array of neurochemicals. These can be broadly divided into two classes: neurotransmittters and neuromodulators. The neurotransmitters, such as glutamate, acetylcholine, and GABA, respond rapidly to retinal stimulation [24]. On the other hand, neuromodulators, such as dopamine, seratonin, and neuropeptides

[24], act over a longer period, and in addition, may cause changes in the neuronal synapses [25]. Synaptic plasticity has been attributed to underlie most hypotheses of neuronal development, neuronal circuit reorganization, and even learning and memory [25]. An example of such an effect in the retina can be seen in the interplexiform cells in the retina [24]. These neurons, which contain dopamine, receive their inputs from the amacrine cells in the inner plexiform layer, and then send their outputs back to the horizontal cells in the outer plexiform layer [24]. Two effects on the horizontal cells have been observed following administration of dopamine: a reduction in light responsiveness, and a decrease in electrical coupling between horizontal cells. Dopamine serves as a neuromodulator rather than a neurotransmitter because it does not exert its influence by acting directly on the horizontal cell membrane channels. Instead, it acts on enzymes that activate protein kinase A, which adds phosphate groups to specific proteins in the horizontal cell membrane to alter their properties and thereby decrease the flow of current across the membrane [24]. Moreover, because of the center-surround structure of the retina, the interplexiform neurons respond in a graded manner to local retinal-image contrast [24].

Therefore, we propose that the result of dopamine administration is a relatively long-term (months to years) reduction in sensitivity to local-image contrast. This mechanism of centripetal feedback via the interplexiform cells can serve to regulate and maintain a relatively constant long-term steady-state operating level and permit relatively normal transient (integrated over hours to days) responsivity to changes in local-image contrast. For example, if the steady-state defocus is set at a certain large amount by, for example, the imposition of high plus or minus lenses, there would be a relatively large release of neurotransmitters and neuromodulators, and thus the retinal response would initially operate at a high output level. However, the feedback mechanism would eventually reduce the steady-state responsivity, so that the responses of neurons at and above the inner plexiform layer would return to nearly normal operating levels. This would permit relatively short-term (hours to days) responses of retinal neuromodulators to reflect accurately any changes in local image contrast. Without such a feedback mechanism, the response would consist of a large steady-state component that would be relatively insensitive to small changes in local-image contrast. Therefore, this feedback regulation mechanism helps to shift the

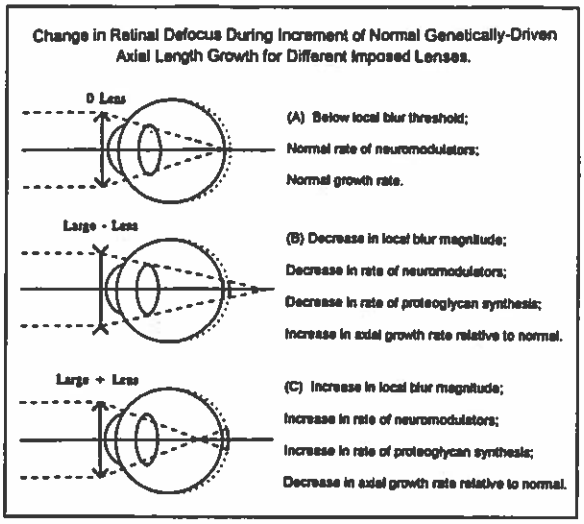

Figure 1. Schematic representation of change in blur circle during a small increment of normal genetically-driven ocular growth under the conditions of: (A) zero lens; (B) minus lens; and (C) plus lens.

steady-state operating level to permit detection of the change in magnitude of retinal defocus, even for a large initial magnitude. In addition, no memory of previous blur level is required because the feedback regulation automatically adjusts itself to attain a long-term steady-state level of sensitivity. Thus, it is proposed that after a steady-state level has been attained, a transient increase or decrease in defocus would result in an increase or decrease, respectively, in the rate of release of neuromodulators as well as the rate of proteoglycan synthesis. Since proteoglycan synthesis is associated with the structural integrity of the sclera, this results in a decrease or increase, respectively, in the rate of axial growth [8,26]. The net effect is that the change in the retinal defocus magnitude, and in turn the rates of release of neuromodulators and proteoglycan synthesis, are in the opposite direction as the change in the rate of axial growth relative to normal. Thus, during an increment of ocular growth (over days), this ability to detect a change in retinal defocus magnitude provides the directional information needed for modulating structural changes in the sclera [8, 26], and in turn regulating the rate of ocular growth.

(3) Overall mechanism for regulating the rate of axial length growth

During ocular development, the eye exhibits continuous genetically-driven growth. The introduction of either plus or minus lenses simply acts to modulate this genetically-determined normal growth

rate. How this modulation occurs can be illustrated by the following example. Consider the effect of introducing lenses in front of the eye. The change in size of the blur circle during a small increment of normal ocular growth for large imposed zero, minus, and plus lenses is shown schematically in Figs. 1A, B, and C, respectively. A neuromodulator, such as dopamine, maintains a certain level of activity related to retinal-image contrast by means of the local retinal feedback mechanism described earlier. For a zero power lens, there is no change in the size of the blur circle, so no additional neuromodulator is released, and the normal genetically-based axial growth pattern of the young eye is continued. For a minus lens, the size of the blur circle is decreased, and thus the rates of neuromodulator release and in turn proteoglycan synthesis are decreased, thereby resulting in an increase in axial growth rate [7]. And, for a plus lens, however, the size of the blur circle is increased, and thus the rates of neuromodulator release and in turn proteoglycan synthesis are increased, thereby resulting in a decrease in axial growth rate [7]. Hence, a decrease or increase in mean retinal-defocus magnitude during an increment of axial growth is proposed to cause a change in the level of the neuromodulator, which in turn leads to structural change in the sclera [8,26] that is manifest as an appropriate change in the rate of axial growth.

The schematic analysis presented above is primarily concerned with the condition of large imposed plus or minus lenses over the eyes. How does this mechanism operate under the condition of long-term nearwork, as in the case of the development of school myopia, where relatively small amounts of retinal defocus are present over extended periods of time? This can be understood by examining the accommodative stimulus/response (AS/R) function [27,28]. This function is an s-shaped curve showing slight over-accommodation at distance and under-accommodation at near. Thus, during nearwork, which is represented by a relatively large accommodative stimulus, the accommodative response lags the stimulus, i.e., it exhibits chronic hyperopic defocus (see Fig. 2). Consider the effect of nearwork during normal genetically-driven ocular growth and exaggerate the effect (i.e., over a larger accommodative range) for illustrative purposes. Let the near target be at a fixed distance, so that the accommodative stimulus and response are given by the solid circle near the arrow designated by the number 3. Following an increment of normal axial length growth, the effective axial length

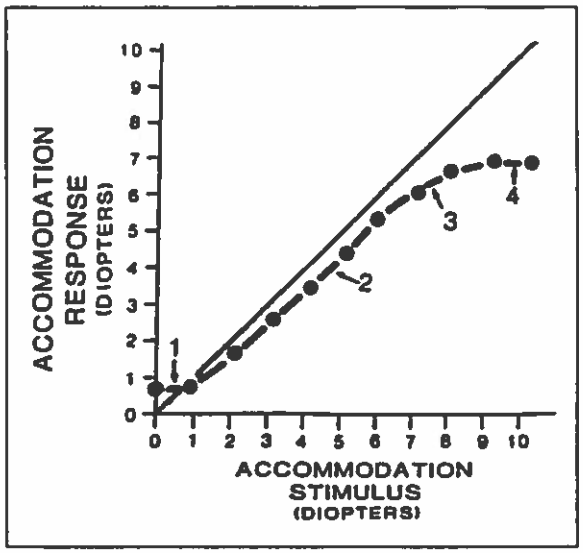

Figure 2. Schematic representation of the static accommodative stimulus-response curve for a typical normal subject. 1 = initial non-linear portion, 2 = linear region, 3 = transitional soft saturation region, and 4 = hard saturation region. Adapted from Cluffreda and Kenyon [29] with permission from the authors.

optical power will have decreased, so that the effective accommodative stimulus (or the optical power needed to focus onto the retina of the incrementally lengthened eyeball) will have also decreased. Thus, less accommodative response would be necessary for clear retinal imagery. This is equivalent to moving slightly downward and to the left on the AS/R function, to arrive at, for example, the next solid circle. The smaller accommodative error is now associated with a proportionally smaller amount of defocus blur. And, according to the same arguments above regarding large imposed minus lens, there would be a proportional decrease in the rate of neuromodulator release, albeit a relatively small amount but persists over a prolonged period, which in turn would result in a decrease in proteoglycan synthesis, with an associated decrease in the structural integrity of the sclera, thereby resulting in an increase in ocular growth rate relative to normal. This assumes that the threshold for defocus-induced ocular growth, which differs slightly for the four refractive groups (hyperopia, emmetropia, early-onset myopia (< 15 years of age), and late-onset myopia (≥15 years of age)) [11], has been exceeded. Moreover, note that the reduction in accommodative error during an increment of genetically-driven ocular growth is more pronounced for near viewing (e.g., point 3) than for far viewing (near point 1), which explains why the subsequent increase in axial elongation rate is primarily associated with near viewing.

Thus, with prolonged nearwork under normal visual feedback, an increment in normal ocular growth results in a change in retinal defocus that causes a compensatory increase in ocular growth rate, and if uncorrected, this process will repeat itself and eventually lead to a progressive development of myopia.

CONCLUSIONS

Our schematic analysis provides a relatively simple and logically-consistent explanation for the eye's ability to grow in the appropriate direction for an imposed experimental lens and the resultant change in retinal-image contrast. This analysis is also applicable to naturalistic changes in retinal defocus, as occurs with chronic accommodative error during prolonged nearwork. The critical point is that the detection mechanism does not depend on the sign of the blur, but rather on the change in blur magnitude during ocular growth. And, it is not necessary to invoke more complicated processes, such as sensing and analyzing of chromatic aberration, spherical aberration, spatial gradient of blur, or spatial frequency content [27,28]. Thus, our hypothesis provides increased understanding of the underlying retinal mechanisms for detecting blur magnitude, and how this signal is processed to modulate the rate of eye growth, and in turn the resultant development of axial myopia.

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