AXIAL, CHOROIDAL AND REFRACTIVE RESPONSES TO MYOPIC DEFOCUS INDUCED BY SPECTACLE LENSES VERSUS PRIOR FORM DEPRIVATION IN CHICKS

A thesis presented to the graduate faculty of
The New England College of Optometry in partial fulfillment
of the requirements for the degree of Master of Science

Vandhana Sharda

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Vandhana Sharda, O.D.

This manuscript has been read and accepted by the Thesis Committee in satisfaction of the thesis requirement for the degree of Master of Science

6/15/2010
Date

Debora Nickla, PhD
Graduate Faculty Advisor

Chea-su Kee, PhD

Frances Rucker, PhD

Frank Thorn, OD, PhD

6/28/2010
Date

Nancy J. Coletta, OD, PhD
Director of Graduate Studies

The New England College of Optometry

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Abstract

Purpose. In chicks, form deprivation and spectacle lens wear have shown rapid compensatory ocular growth changes. This emmetropization is strongly linked to the visual signal of defocus. In order to determine if eye shape plays a role in emmetropization, we examined the response to myopic defocus induced by prior form deprivation versus that induced by positive spectacle lenses.

Methods. Recovery: 33 Chicks were monocularly form deprived for one week, for the next 7 days they were allowed 12 hours of vision (n=13), 4 hours of vision (n=7), 2 hours of vision (n=7) or 0 hours of vision (n=6). *Positive Lenses/Deprivation*: 12 Chicks were form deprived and allowed 2 hours per day of +10D lens wear for 7 days.

Results. In recovering eyes, 2 hours of unrestricted vision was as effective as 12 hours of unrestricted vision in inducing refractive and axial length compensation. Conversely, 2 hours

of spectacle lens wear alternating with form deprivation was not sufficient to induce a refractive or axial length response.

Conclusions. Two equivalent myopic defocus signals did not produce equivalent ocular or refractive changes. The larger eye of the prior form deprived chicks showed a more robust compensation to the blur signal than did the positive spectacle lens paradigm. Thus these two paradigms have a different underlying mechanism and demonstrating that a size component is involved in the emmetropization process.

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Introduction

It is generally accepted that growing eyes use visual input to guide their growth toward emmetropia, a state in which distant objects are focused onto the retina. This process has been illustrated during recovery from form deprivation[1] and negative lens wear[2] which both result in the development of axial elongation and myopia in chicks. The imposition of form deprivation on the chick eye by the use of translucent diffusers prevents both spatial and temporal transients, with the result that the eye grows in a "default" direction, enlarging to become myopic[1]. This "default" growth is believed to be the result of the absence of an error signal during form deprivation thus creating an "open loop" condition without visual feedback, which results in high myopia. When the vision is restored and the diffuser removed, the distant images are now focused in front of the retina. The chick's eye then changes its growth rate to bring this image toward the retinal plane[3] and "recovers" from the induced myopia in the process of emmetropization.

Other species show varying responses to form deprivation. For instance, in the American kestrel[4] form deprivation causes less myopia than in the chick eye, with hyperopia in some. Although the untreated eyes are similar to that of control birds, a finding also reproduced in chick studies, the degree of myopia development and eye enlargement of the form deprived eye is minor. The treated eyes of the American kestrel are also able to reach emmetropia like the chick eye, in this case within 10 days, after being given unrestricted vision. Of note is that this avian species is highly myopic at hatching while the chick is hyperopic thus the Kestrel's direction of growth toward emmetropization is in the opposite direction to that of the chick. In other mammalian species such as the marmoset[5, 6], rhesus

macaque [7, 8] and tree shrew[9], form deprivation also produces myopic growth. Similar to the chick, these treated eyes develop longer axial lengths and are considerably more myopic than untreated eyes. And in contrast to the chick, these treated eyes remain myopic for many years after regaining unrestricted vision although there are some exceptions for the tree shrew. In the kitten which begins as slightly hyperopic, like chicks, form deprivation induces hyperopia[10]. This is true in kittens as well as adult cats, and more strongly seen in dark reared than light reared conditions in which some low myopic shifts are seen in lid sutured eyes. This change in refractive error is effected by a change in growth rate and corneal curvature, the latter of which is not seen in the chick eye.

On the other hand, when chick eyes are outfitted with negative spectacle lenses, the incident light comes to a focal point behind the retina, creating a functionally hyperopic eye.[2] In response, the eye elongates to move the retina towards the image plane in order to obtain a clear image, and hence emmetropia.[11] The initial lens-induced hyperopic defocus in this "closed-loop" condition allows the eye to compensate to the refractive error by use of negative feedback, and so the end myopic refractive error is proportional to the dioptric strength of the negative inducing lens.[12] Thus the use of negative lenses on a chick eye results in ocular growth patterns which ultimately result in a myopic eye. Positive lenses converge incoming light in front of the retina initially creating a myopic eye which also produces a compensatory hyperopic change in growth rate to move the image onto the retinal plane[11] as well as recovery with emmetropia. Thus the use of positive lenses on a chick eye results in ocular growth patterns which ultimately result in a hyperopic eye.

Mammalian models have also shown eye growth patterns with spectacle lens wear. Rhesus monkeys reared with negative contact lenses develop axial myopia[13] in most cases which recover back to emmetropia once the contact lens is removed. A similar hyperopic compensatory growth pattern to ultimately result in myopia is also seen in both rhesus monkeys[14] and tree shrews[15] who are raised with negative spectacle lenses[14]. Similar to the chick eye, rhesus monkeys show compensation and recover to both negative and positive spectacle lens wear[14]. Each of these studies reveals that results depend on the magnitude of the inducing lens and the amount of defocus time given.

Two components of compensation to retinal defocus

There are two separate, but possibly mechanistically-linked, components of compensation to image defocus, a scleral one, in which changes in the synthesis of extracellular matrix result in changes in the growth rate and hence size of the eye [16], and a faster choroidal one in which changes in the thickness of the choroid moves the retina back or forward, towards the image plane[17].

Specifically, in eyes wearing positive lenses, the image falls in front of the retina so the choroid begins to thicken within hours of the stimulus, and then a day or two later, the eye growth ceases, until the eye becomes emmetropic. If the lenses are then removed, the opposite changes occur to restore emmetropia. Conversely, in eyes wearing negative lenses, the image falls behind the retina, so the choroid thins, and following a lag of several days, the ocular elongation increases again to restore emmetropia[11].

Because form deprivation is an open loop condition, the default state is excessive eye growth. However, in this case as well, the choroid thins, similar to that of the negative lens-wearing eyes. Again, similar to the lens conditions, when the occluder is removed and the eye experiences a large myopic defocus, the choroid quickly thickens, and the growth ceases, allowing "recovery" from the diffuser-induced myopia. That this response is visual is evidenced by the finding that this recovery does not occur under conditions of dim illumination.[18]

Despite their different visual stimulus characteristics and because both form deprivation and negative lens-wear result in axial elongation, choroidal thinning and myopia, it is possible that the mechanisms underlying the excessive growth are similar. In support of similar underlying mechanisms, the excessive elongation produced by both can be inhibited by giving the eye brief daily periods of unrestricted vision.[19,20,21] However, there is more evidence that supports different underlying processes. For instance, the use of 6-hydroxy dopamine, which interferes with dopaminergic pathways, inhibits the development of form deprivation myopia but has no effect on negative lens-induced myopia.[22] However when this experiment was repeated with higher powered negative lenses some inhibition of axial length growth was noted from the 6-hydroxy dopamine use.[23] Second, optic nerve section did not affect the development of myopia in response to form deprivation, but did inhibit that induced by negative lenses.[11] Finally, negative lens wear stimulates increased ocular elongation within 25 hours while form deprivation requires 3 days.[24]

Another line of evidence for differences is reflected in the response to light/dark manipulations. Brief bursts of strobe light during the day significantly inhibits the induced

myopic effects, refractive error and axial length growth, from form deprivation while having a negligible affect on that produced by negative lenses. Conversely if brief periods of light are given during the dark night hours, induced myopia and axial length growth from negative lenses is inhibited more than that from form deprivation.[24]

What about the myopic defocus produced by removing a diffuser from an eye that had been deprived of form vision, versus that produced by wearing a positive spectacle lens? Both of these conditions are closed-loop: there is an error signal to which the eye can respond. However, there is a difference: in the case of the spectacle lens, myopic defocus is being imposed on an eye of "normal" size/shape, whereas in the case of removal of the diffuser, the myopic defocus is imposed on a highly-enlarged eye. Thus, if there is a "shape" component to emmetropization, these larger eyes might respond faster than those that receive just the "visual" signal. Support for the visual regulation of eye growth being stronger than the "shape" one, is the fact that emmetropization is halted if a correcting negative lens replaces the occluder. This recovery will be limited to the value of the correcting lens. [25, 26]

Temporal Aspects of Compensatory Responses

It has long been known that the effects of form deprivation can be effectively reversed by only an hour or so of daily unrestricted vision (presumably myopic defocus), indicating a long integration time for the myopiagenic stimulus. After 130 minutes of unrestricted vision, 95% of the induced myopia from continuous occluder wear can be prevented in chicks.[20]

The eye shows a remarkable ability to respond to defocus in both directions: it requires only short intervals of exposure to defocus to compensate: only a few minutes of

defocus, especially if given as frequent short intervals, are sufficient for lens compensation in both directions (plus and minus). However, the temporal integration of hyperopic and myopic blur induced by lenses have been shown to differ: while eyes must wear the negative lenses almost continually for ocular growth compensation, only short amounts of daily myopic blur (positive lenses) seem sufficient to induce compensation.[21] As little as 8 minutes of positive lens wear after a full day of negative lens wear results in compensation towards the positive lenses. Furthermore, when positive and negative lenses are alternated over the course of the day, the positive lenses have a much greater effect than the negative lenses. Indeed, even a few minutes of positive lens-wear four times a day can balance out the remainder of the day wearing negative lenses. This implies nonlinearity between the processes underlying positive and negative lens wear compensation.[27] Finally, this asymmetry in the efficacy of the positive and negative lenses depends on the frequency of alternation: if myopic and hyperopic defocus are alternated several times a second, the asymmetry disappears.

Positive lens wear and vision following form deprivation both produce a myopic defocus in the chick eye. If a positive lens replaces the occluder during recovery from form deprivation then both myopic defocus error signals trigger an increase in ocular growth. Thus form deprivation and positive lens wear have a similar underlying mechanism. Support of this is seen with optic nerve section which does not inhibit the ocular response to either indicating they are both locally controlled.[11, 28]

Is there really bidirectional compensation of defocus? Because myopic defocus can be cleared by the viewing of near objects, it is possible that the changes in eye growth in response to both myopic and hyperopic defocus are the result of the total amount of blur

produced, with eye growth being proportional to the blur (the “blur hypothesis”). Hence, the eye would continue to grow until the blur induced by the hyperopic defocus is eliminated. However, an eye exposed to myopic defocus would experience some clear vision with near objects, and so the eye would not slow its growth in proportion. The evidence against this however, is that when accommodation is paralyzed, and the viewing distance is controlled so that chicks experience only near or far objects, there is still compensation in both directions. This suggests that the myopic blur itself is the trigger for changes in ocular growth patterns.[29]

This process of compensation for blur induced by positive or negative lenses occurs even when the chick’s accommodative system (focusing) system is in-operational[30] and when the optic nerve is cut indicating that this process may be controlled by factors within the ocular environment.[28] Although this emmetropization process is coordinated locally, it is more accurate when the optic nerve is intact as experimental values of axial length and refractive error when the optic nerve is severed have similar trends but more variable results.[26]

Because evidence suggests that form deprivation and negative lens wear may have different underlying mechanisms, we questioned whether the responses to myopic defocus induced by prior form deprivation versus that induced by positive lens wear may also differ. These conditions have a common visual signal, that of myopic defocus, but in the case of prior form deprivation, the eye is abnormally large while in the case of lens wear the eye is of “normal” size, and so would address the issue of the ability of the eye to use a “shape”-driven signal. These experiments examined the temporal integration characteristics of the responses in chick eyes that had been previously form deprived and compared them to eyes wearing

positive spectacle lenses. By comparing the extent and strength of the axial and choroidal compensation we hope to gain insight into the underlying mechanisms of the emmetropization system.

Methods

I Form Deprivation "Recovery"

Thirty-three White Leghorn chicks (*Gallus gallus domesticus*) were raised from one day old in temperature-controlled brooders under normal visual conditions. The light cycle was 12L/12D. Food and water were supplied ad libitum. On the fifth day all chicks had their right eyes occluded. This was done using collodion glue to adhere a Velcro ring around the outside of the right eye. The Velcro counterpart was glued to a half sphere shaped translucent occluder, which allows light to pass through but diffuses the image. This set up allowed for the easy removal and replacing of the occluder in order to take multiple measurements of the eyes. The left eyes served as untreated controls. The eyes remained occluded over 7 days (i.e. undergoing form deprivation). Subsequently, the occluders were removed for various time intervals over the course of 7 days (12 hours, 4 hours, 2 hours, and 0 hours, see below). Also over this same week, the eyes were measured using high-frequency A-scan ultrasonography (for details see below) and all chicks were measured for refractive error using streak retinoscopy.

For the recovery paradigm, beginning on day 8 of form deprivation, the birds were divided into 4 groups. Thirteen chicks were then allowed full vision (12 hours/day) in the experimental eye by permanently removing the occluder (12 hour group). A second group

were given four hours of vision per day (n = 7) in the middle of the day, a third group were given two hours of vision (n = 7) per day in the middle of the day, and a fourth were not given any unoccluded vision (n = 6). Repeated measures of refraction and ultrasound were taken over the following week on days 1, 2, 3, 5, and 7, for all groups, immediately following the period of vision during which they experienced the myopic blur.

II Plus Lens/Deprivation

Twelve White Leghorn chicks (*Gallus gallus domesticus*) were raised from one day old in temperature-controlled brooders under normal visual conditions. At day 12, occluders were put on the right chick eye as above, allowing the left eye to serve as the untreated control. Over the next seven days, for two hours a day, between the hours of 1pm and 3pm, a +10 diopter lens was mounted in place of the occluder (n = 12). At the end of the two hours each day, the occluders were replaced. All left eyes in the 12 birds served as untreated controls. Measurements were taken as below with a retinoscope and ultrasound on days 1, 2, 3, 5, and 7. Ultrasound measures were taken both immediately before and after the plus lens wear on days 2 and 3 to measure any changes in ocular axial dimensions occurring during the short interval of lens wear.

III Measurement Procedures

(a) Retinoscopy

Chicks were put under isoflurane (0.8%, in oxygen) anesthetic in order to perform both measurement procedures. The chicks lay on a measurement bed and were gently

secured down while being administered the anesthetic. The experimenter, using a Welch Allyn retinoscope, performed the refractions. Light from the retinoscope was directed into the eye of the chick. Based upon the movement, the reflexes were neutralized with free lenses until movement was no longer perceived. A light reflex moving in the direction the retinoscope, was neutralized using progressively stronger plus lenses until no movement was seen. This was performed in two meridians, 90 degrees apart, in each eye. The neutralizing lens values were recorded for both meridians and later reduced to spherical equivalent form by taking the average measure of both meridians. Progressively stronger negative lenses were used for neutralization in the same manner if the light reflex was seen to move in the opposite direction to the retinoscope. Relative differences between each experimental group were compared, as a result although the "small eye artifact" was not taken into account this likely did not affect the outcome.

(b) Ultrasound

Next, high-frequency A-scan (30 MHz) ultrasonography was performed. Ultrasound gel was applied to the chick eye before an ultrasound probe was aligned with the pupillary axis of the eye. Once in proper alignment, about 8-10 traces were captured, averaged and analyzed. The vitreous chamber was determined to be from the posterior lens to the anterior retina. The axial length was determined to be from the anterior cornea to the anterior sclera. This allowed for the analysis of any changes within the choroid alone. The chicks' recovery from the anesthetic generally occurred within minutes.

Results

I. Recovery Experiment: Myopic defocus induced by prior form deprivation

Axial Length

It was found that as little as 2 hours of unrestricted vision per day for 7 days was as effective at inducing axial compensation to the myopic defocus as full (12 hours per day) unrestricted vision (Figures 1 and 3). As seen in Figure 1, there was no difference between any of the groups getting vision (2, 4 or 12 hours) in the axial length on the last day of the experiment (10.71 mm, 10.83 mm, 10.46 mm, respectively, Figure 1a). As expected, the fully-deprived eyes (0 hours vision) continued to elongate at a faster rate than any of the other groups, and the eyes became significantly longer (11.41 mm; $p<0.05$ compared to all others; ANOVA, $p<0.005$; Figure 1a).

When the rates of growth per interval were examined (Figure 1b), there were no differences between the groups given daily vision at any of the intervals except the first 24 hours; this is due to an unexplained, unusually high growth rate for the 4 hour group (note the larger standard error as well). Note that while the fully deprived eyes continue to grow at a faster than normal rate (Figure 1b, compare black bars to circles) at all intervals, by 3-5 days all vision groups are growing at a significantly slower rate than the fully deprived eyes. At days 5-7 all of three vision groups were growing at a slower rate

than the untreated, contralateral control eyes (36µm, 32µm, 29 µm/day vs 99 µm/day, respectively, Figure 1b; ANOVA, $p<0.001$).

Choroidal Thickness

The choroids of eyes getting limited amounts of myopic defocus per day (2 and 4 hours) increased in thickness by an amount intermediate between no change (0 hour group) and the unrestricted myopic defocus (12 hours) (Figure 2). As expected, based on previous studies, the choroids of form deprived eyes getting unrestricted vision (therefore experiencing myopic defocus) show a significant and rapid thickening over the 7 days of visual exposure (change in thickness, 450 µm, Figure 2, black squares). In contrast, choroids of eyes getting either 2 or 4 hours of daily unrestricted vision showed a partial thickening in response to the myopic defocus (175 µm and 217 µm, respectively, Figure 2). Choroids of form deprived eyes (0 hours) are thinner than normal at the start (from the prior 7 days of form deprivation) and remain thinner than normal (98 µm to 104 µm, Figure 2). At day 7, there is no significant difference between the thickness of the choroids from the 2 hour and 4 hour vision groups (387 µm and 365 µm, respectively). However, they are both significantly thinner than those of the 12 hour group (638 µm, $p<0.01$), and significantly thicker than the 0 hour group (104 µm, $p<0.001$).

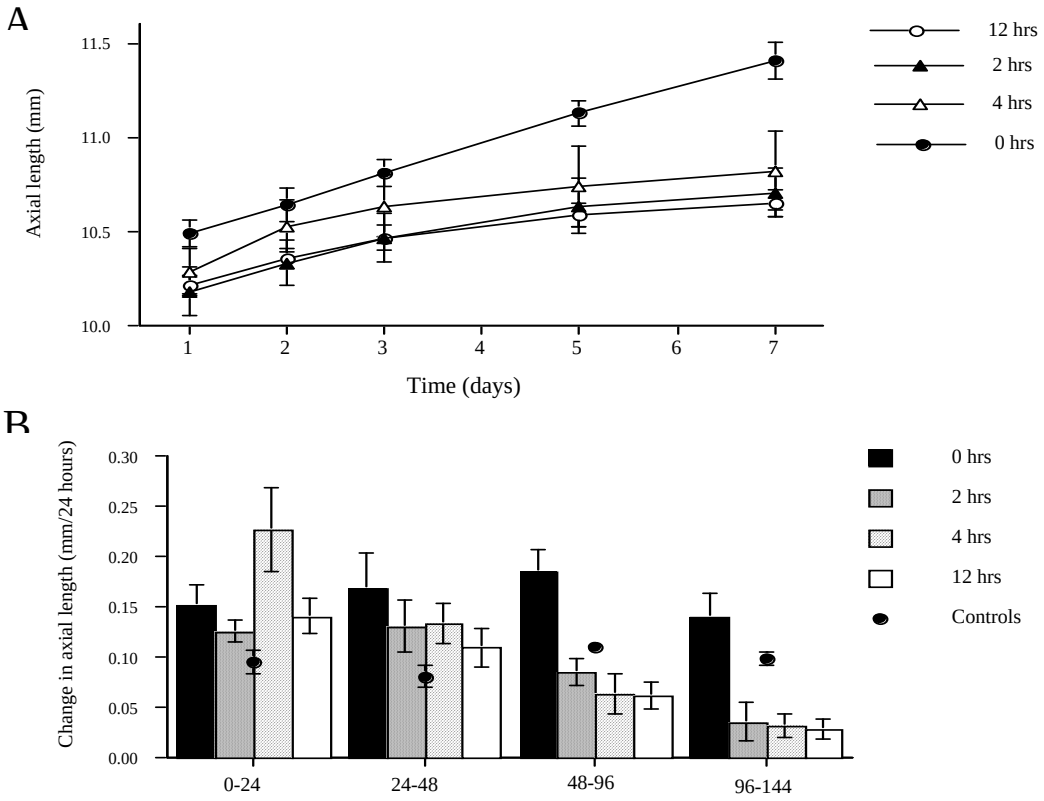


Figure 1. Change in axial length. A. Change in axial length in eyes with daily diffuser removal for 0, 2, 4 hours, or all day (12 hours) over the 7 days. B. Change in length per 24 hour period (growth rate) over various intervals. Note that all groups given any amount of daily defocus slow their growth rate on the third day.

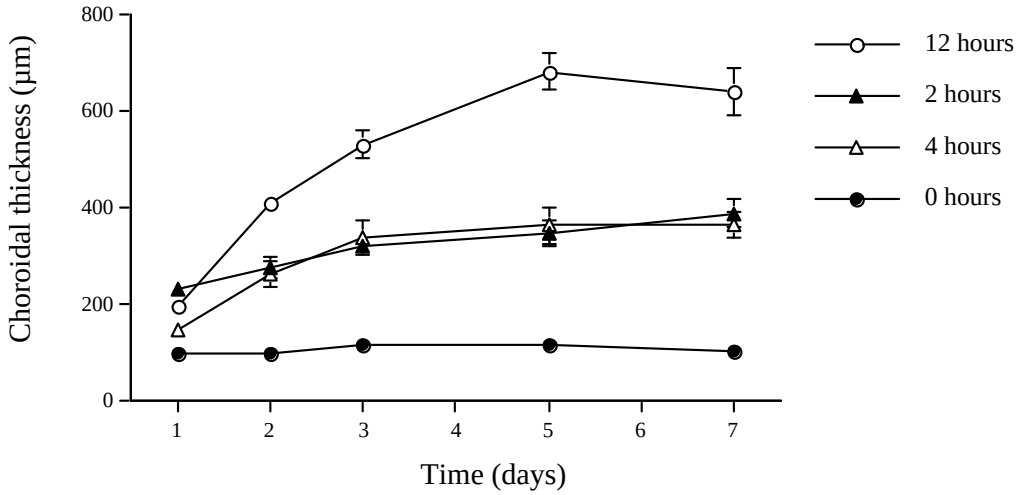


Figure 2. Change in choroidal thickness over the course of 7 days. Note that choroids of eyes receiving either 2 or 4 daily hours of myopic defocus show thickening intermediate between eyes receiving no defocus (0 hours) and a full day of defocus (12 hours).

Vitreous Chamber Depth

The effect on the vitreous chamber depth is the result of both the effects on growth rate (axial length) and on choroidal thickness (Figure 3), with the assumption that there is no change in anterior chamber depth and lens thickness. Specifically, for eyes getting no visual exposure (0 hours), the increase in vitreous chamber depth is a reflection of the increase in axial length (as in normally developing eyes) because there is no significant choroidal contribution. Conversely, in the recovering eyes getting 12 hours per day of myopic defocus, the continued increase in choroidal thickness, along with the decrease in axial elongation, results in a decrease in vitreous chamber depth (gray squares, Figure 3). For the partial vision groups (2 and 4 hours vision) the intermediate increase in choroid thickness together with the decrease in growth rate result in essentially no change in the

vitreous chamber depth. There were no significant differences at any of the times for the 2 and 4 hour vision groups, except at the first time point.

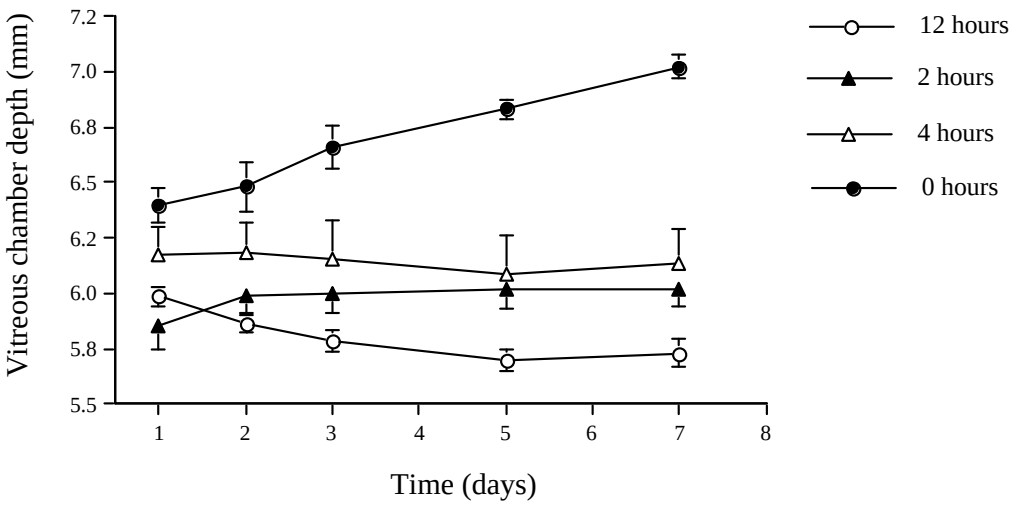


Figure 3. Change in vitreous chamber depth over the course of 7 days. Note that vitreous chamber of eyes receiving either 2 or 4 daily hours of myopic defocus show essentially no increase, and remain intermediate between eyes receiving no defocus (0 hours) and a full day of defocus (12 hours). This effect is due to the thickening of the choroid in these two groups.

Refractive Error

The changes in the refractive error during the course of the experiment mirrored the anatomical changes (Figure 4). During recovery from form deprivation, a full 12 hours of vision produced full compensation (a change of +13.3 D) while merely 2 hours of unrestricted vision per day produced a change of +10.1 D (non-significant) (Figure 4). When compared to the 2 hours of positive lens wear/deprivation eyes, there was a slight myopic shift -2.5D which was similar to the contralateral control eyes -0.2 D (-2.5 D vs -0.2D, $p < 0.05$; Figure 4)

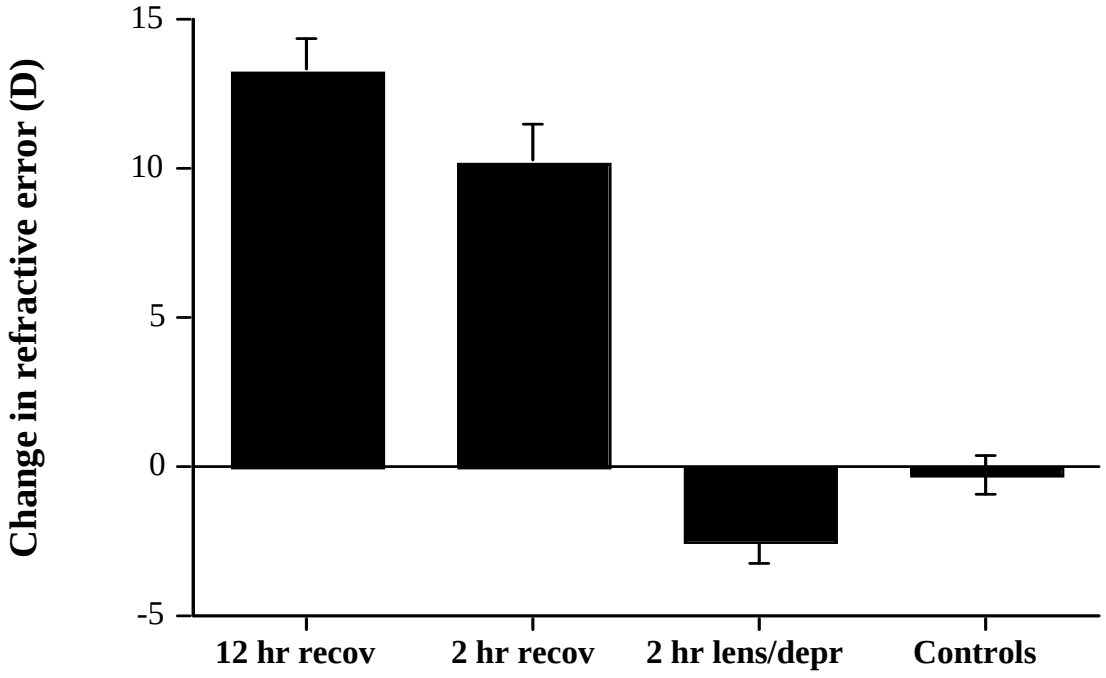


Figure 4. Change in refractive error over the course of 7 days. Eye receiving full daily myopic defocus and only 2 hours of defocus show a large hyperopic change over the 7 days. While the eyes receiving 2 hours of plus lens wear alternating with deprivation show a small myopic shift. Contralateral control eyes also show a minimal myopic shift.

Four hours of vision data was not included as it is presumed the results would be similar to both 12 and 2 hours of vision groups as all axial length measures were the same by the end of the experimental period.

II. Positive Lens Experiment: Myopic defocus induced by positive lens wear

Axial length

Eyes exposed to 2 hours of daily lens-induced myopic defocus alternating with form deprivation (lens/occluded), did not compensate for the myopic defocus; in fact, they

grew slightly (but not significantly) longer than contralateral control eyes (Figure 5A), and became slightly myopic (-2.5 D). When the rates of growth were evaluated against the comparable eyes given 2 hours of (deprivation-induced) myopic defocus, it is apparent that the two responses differ from each other (Figure 5B). On the first day of myopic defocus, eyes from the "recovery" paradigm were growing significantly faster than the eyes getting the lenses alternating with deprivation (126 μm vs 62 μm/day, $p<0.01$; Figure 5B). This presumably reflects the lag time for the previously form deprived eyes to slow their growth (3-4 days are required). There is no significant difference in growth rate over the first 24 hours between the eyes getting lens-induced defocus and contralateral control eyes (62 μm vs 95 μm, respectively). On the subsequent two intervals, the lens/deprived eyes begin to increase their rate of growth while the recovering eyes slowed their growth (compare striped to solid bars, Figure 5B). By the final day, the lens/occluded eyes were growing significantly faster than control eyes (129 μm vs 99 μm/day; $p<0.05$) while the recovering eyes were growing significantly slower than controls (36 μm vs 99 μm/day; $p<0.05$). The rates for both experimental groups were significantly different (36 μm vs 129 μm/day; $p=0.001$).

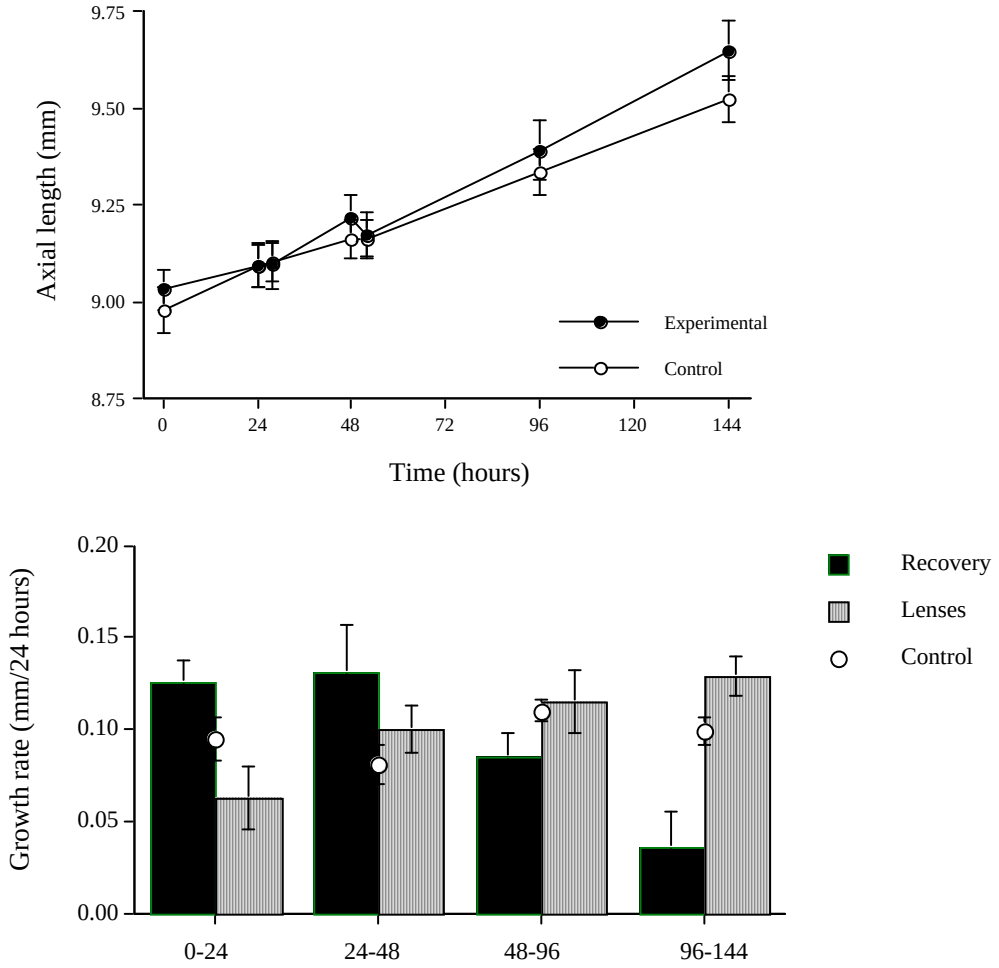


Figure 5. Changes in axial length in positive lens wear and in comparison to prior form deprivation. A. Change in axial length in eyes receiving 2 hours of lens-induced defocus alternating with form deprivation. B. Rates per 24 hours in previously form deprived eyes getting 2 hours of myopic defocus per day (recovery) compared to eyes wearing positive lenses for 2 hours/day, alternating with form deprivation. Eyes in the lens paradigm do not decrease their rate of growth over the 48-144 hours; the recovering eyes do. Fellow controls are shown as symbols for comparison.

Choroidal Thickness

In contrast to the thickening choroids of recovering eyes receiving 2 hours of myopic defocus per day, choroids of lens/occluded eyes decreased in thickness (-158 µm overall, Figure 6A, solid symbols; compare to Figure 2, gray triangles). This decrease in thickness

was significantly greater than the normal developmental thinning seen in the contralateral control choroids (-158 µm vs –58 µm; $p<0.05$). Note however, the transient thickening over the 2 hours of myopic defocus on days 2 and 3 (Figure 6A and B).

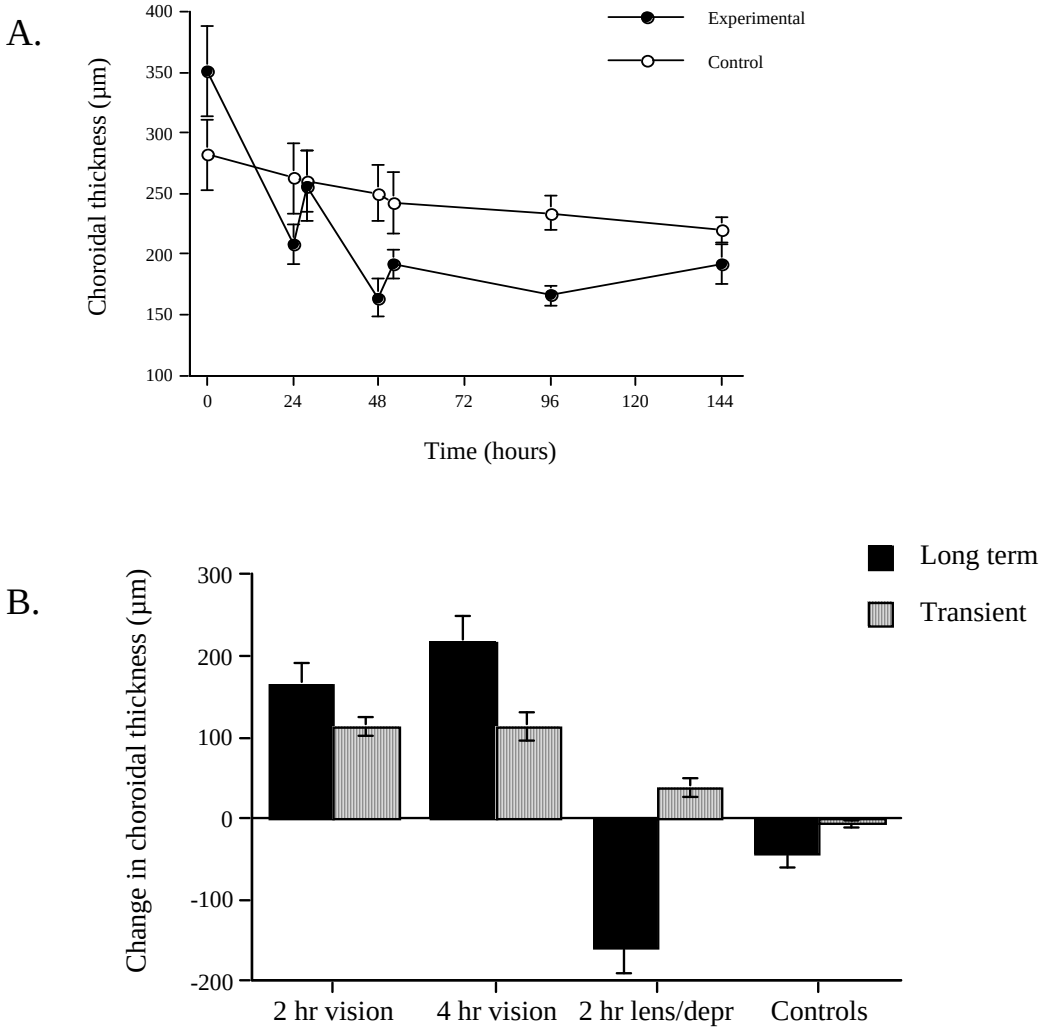


Figure 6. Changes in choroidal thickness during positive lens wear and in comparison to prior form deprivation. A. Change in choroid thickness over the course of the experiment. Note that the experimental eyes decrease in thickness, but show transient increases over the course of the exposure to defocus. B. Changes in thickness over the course of the experiment ("long term") versus transient changes over the 2 hours of exposure ("transient"). Note that there are transient changes in all groups, but the lens-condition did not show "summation", and instead thinned.

Transient Effects

Despite the overall lack of compensation to the myopic defocus induced by the daily lens wear, both in axial length and choroidal thickening, there was a transient response for both parameters (Figures 5A and 6A). When the eyes were measured immediately before and after the period of plus lens wear on the second and third days of treatment, it was found that there was a decrease in axial length (Figure 5A) and increase in choroidal thickness (Figure 6A) over the 2 hours. The axial length decreased by -8 μm and –24 μm on the two days respectively (Figure 5A: mean = -12 μm). This difference almost reached statistical significance when compared to the change in length of control eyes over the 2 hour exposure (Figure 5A, compare symbols; -12 μm vs +11 μm; $p=0.06$). In addition, the choroid increased in thickness by 48 μm and 28 μm on the two days (Figure 6A: mean = 38 μm). This was significantly different from the change in choroidal thickness in control eyes (Figure 6B, compare symbols; 38 μm vs -5 μm: $p<0.005$).

Discussion

Previous work suggests that the dynamics of the responses of eyes to form deprivation differ from those to negative spectacle lens wear, despite the similarities in the responses, namely the overall increase in growth rate and the thinning of the choroid. Specifically, eyes responding to negative lenses show a faster response, increasing their rate of growth over the first 3 days while eyes wearing diffusers did not show an increase in rate until the third day.[24] There are also differences in the temporal dynamics of the changes in scleral proteoglycan synthesis.

Similarly, there are temporal differences in the responses to myopic versus hyperopic defocus induced by positive and negative lens wear, respectively. Specifically, the compensatory decrease in growth rate in response to positive lenses require only brief daily periods of defocus while the compensatory increase in rate in response to negative lenses requires much longer daily durations of the defocus. [21] These studies suggest that the mechanisms underlying the changes in ocular growth and choroidal thickness differ for diffusers, and for both directions (positive and negative) of defocusing lenses.

To date, however, there have been no reports of differences in the compensatory responses to myopic defocus induced by prior form deprivation versus positive spectacle lens wear. Presented here is the first evidence of differences in the responses to myopic defocus induced by these two different methods. It was found that eyes made myopic by prior form deprivation showed more robust compensation, both axial and choroidal, than eyes made functionally myopic by wearing positive spectacle lenses: only 2 hours per day of defocus was required for the previously form deprived eyes to show compensation while 2 hours of daily spectacle lens was insufficient.

Form deprivation via translucent occluders produces a rapid increase in ocular elongation and concomitant development of myopia; this is true for all species tested to date. These studies constitute the first evidence for the visual (environmental) regulation of ocular growth. However it was not evidence for active visual emmetropization. It has been postulated that the response to form deprivation was the result of the regulatory mechanisms running open-loop, as there was no signal on which visual feedback could operate. Interestingly, if only a partial occluder is worn by the chick and then alternated with

unrestricted vision, only the occluded area of the choroid compensates by thickening.[14] By contrast, when the diffusers were removed, the myopic defocus experienced by the eye provided an error signal causing a compensatory decrease in ocular growth rate via a visual feedback regulatory mechanism. This was the first evidence for active emmetropization in the mammalian model, although similar evidence had been found earlier in the chick.[2,12] Similarly, the compensatory growth responses to both negative and positive spectacle lenses strengthened the evidence for the visual regulation of eye growth.

Given the obvious differences between the visual stimuli (signal) provided by a diffuser and that provided by a negative lens, it is not very surprising that despite the similar end result (i.e. myopia) there appear to be essential differences in the underlying mechanisms producing the growth response [11, 21]. On the other hand, when eyes experience continuous myopic defocus, there were no apparent differences in the responses of eyes that had been made myopic by prior form deprivation versus those made functionally myopic by spectacle lenses; both show a rapid decrease in growth rate and increase in choroidal thickness. However, if the duration of the signal (defocus) is reduced so that the eye experiences only brief daily periods of the signal alternating with deprivation, a large difference in efficacy is uncovered. This difference in efficacy can not be explained by a visual difference: the myopic defocus signal produced by prior form deprivation did not differ in any essential way from that produced by the positive spectacle lenses, except perhaps by a small difference in magnitude. The amount of myopia produced by the prior form deprivation varied somewhat between animals; the mean for all groups was approximately -12 D. The +10D lenses used in the spectacle lens experiments may have produced slightly less magnitude of defocus given

that the chicks would have been slightly hyperopic to start. It is extremely unlikely that the large differences in response characteristics could be accounted for by the small difference in mean starting refractive error. In fact, it has been shown that eyes responding to +5 D respond as rapidly as those responding to +15 D lenses, the only difference being the end refractive error[11]. It would seem that the parameter accounting for these differences in growth response was the size of the eye at the start of the experiment. The eyes that were made myopic by previous form deprivation were abnormally long at the outset of the experiment while the eyes that were made functionally myopic with spectacle lenses were of normal length.

In the experiments reported here, a mere two hours of unrestricted vision (myopic defocus) was required in the previously form deprived eyes to elicit almost complete axial compensation. The eyes slowed their rate of growth significantly by 48-96 hours of the daily exposures; amazingly, there were no differences in growth rates for eyes receiving 12 hours, 4 hours or 2 hours defocus per day. Conversely, when an equivalent blur signal was created using positive lenses (alternating with form deprivation) a dramatically different result was obtained. Under these conditions it was found that the eyes did not compensate to the myopic defocus. In fact, these eyes grew slightly longer and became slightly more myopic than untreated control eyes. In this paradigm therefore, these eyes starting at a “normal” size respond more to the 10 hours of deprivation than the 2 hours of myopic defocus. This difference suggests that different mechanisms underlie the responses to the two equivalent visual signals. The difference is presumably a non-visual one, perhaps related to the size of

the eyes, as the only difference between the two paradigms is that the recovering eyes start out larger at the onset of the periods of myopic exposure.

It has been suggested that the choroidal thickening in response to myopic defocus may play a direct role in the mechanism(s) underlying the compensatory decrease in growth rate in these eyes.[17] Other evidence showing dissociation between the two (axial and choroidal) responses under certain visual conditions has weakened this notion.[31] In the experiments reported here, it was found that while a mere two hours of defocus resulted in nearly full axial compensation (as did four hours), there was only a partial choroidal compensation (i.e. the choroids only thickened by about half the maximal amount when given either two or four hours of vision a day) in the previously form deprived eyes. Therefore, it appears that full choroidal thickening is not necessary to produce the compensatory decrease in the axial growth rate in recovering chick eyes. However, this result does not discount the possible role of the choroid in the growth response; it remains possible that the partial thickening is sufficient to elicit or influence the decrease in growth rate.

In contrast to the eyes that were previously deprived, the choroids of eyes receiving myopic defocus from 2 hours of daily spectacle lens wear did not show any “long term” thickening, in fact, these choroids became thinner than normal over the course of the experiment. This thinning response is consistent with the fact that these eyes became slightly longer and more myopic than untreated eyes, and is consistent with a choroidal effect on axial elongation. Again, the difference in response must be accounted for by the different sizes of the eyes at the outset of the experiment: choroids of these normal sized eyes made

functionally myopic with lenses did not respond to the myopic defocus, but instead, to the form deprivation.

While the 2 hours per day of spectacle lens wear did not produce any overall compensation, a transient response was seen over the two hours of the exposure to the myopic defocus. Within the two hour period there was a decrease in axial length and an increase in choroidal thickness. This rapid and transient compensation was similar to that seen in form deprived eyes which were given brief (two hour) periods of unrestricted vision. This transient effect on both parameters was reversed by the following day (24 hours later). We speculate that these transient responses may play a role in the mechanism underlying ocular growth regulation. The existence of these rapid brief responses necessitates that further studies control for the time of measurement with regard to the visual experience to prevent misinterpretation.

This comparison of the effects of myopic blur signals has produced some intriguing findings. Although identical, the myopic blur resulting from prior form deprivation resulted in a more robust compensation as compared to the myopic blur induced by a high plus lens. The form deprived, larger eyes produced a delayed compensation when as little as 2 hours of vision was given with a decrease in axial length while the choroid thinned. Interestingly, the choroid's response appears to be working with a different mechanism than the axial length as the choroidal response was greater when a greater amount of vision was given. The lens/deprived eyes did not show this compensation to the blur when given 2 hours of vision indicating a different mechanism conducting the response to the signals. A transient

response was seen in the lens/deprived chicks. Further study here may help elucidate the differences in the two pathways.

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