

The Effect of Bright Light on Lens Compensation in Chicks

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PURPOSE. It has been shown that sunlight or bright indoor light can inhibit the development of deprivation myopia in chicks. It remains unclear whether light merely acts on deprivation myopia or, more generally, modulates the rate of emmetropization and its set point. This study was conducted to test how bright light interacts with compensation for imposed optical defocus. Furthermore, a dopamine antagonist was applied to test whether the protective effect of light is mediated by dopamine.

METHODS. Experiment A: Chicks monocularly wore either -7 or $+7$ D lenses for a period of 5 days, either under normal laboratory illuminance (500 lux, $n = 12$ and 16 , respectively) or under high ambient illuminance (15,000 lux, $n = 12$ and 16). Experiment B: Chicks wore diffusers for a period of 4 days, either under normal laboratory illuminance (500 lux, $n = 9$) or high ambient illuminance (15,000 lux), with the bright-light group intravitreally injected daily with either the dopamine D_2 antagonist spiperone (500 μ M, $n = 9$) or a vehicle solution (0.1% ascorbic acid, $n = 9$), with an untreated group serving as the control ($n = 6$). Axial length and refraction were measured at the commencement and cessation of all treatments.

RESULTS. Exposure to high illuminances (15,000 lux) for 5 hours per day significantly slowed compensation for negative lenses, compared with that seen under 500 lux, although full compensation was still achieved. Compensation for positive lenses was accelerated by exposure to high illuminances but, again, the end point refraction was unchanged, compared with that of the 500-lux group. High illuminance also reduced deprivation myopia by roughly 60%, compared with that seen under 500 lux. This protective effect was abolished, however, by the daily injection of spiperone, but was unaffected by the injection of a vehicle solution.

CONCLUSIONS. High illuminance levels reduce the rate of compensation for negative lenses and enhance the rate for positive lenses, but do not change the set point of emmetropization (target refraction). The retardation of myopia development by light is partially mediated by dopamine, as the injection of a dopamine antagonist abolishes the protective effect of light, at least in the case of deprivation myopia. (*Invest Ophthalmol Vis Sci.* 2010;51:5247-5253) DOI:10.1167/iovs.09-4689

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Myopia is a refractive disorder caused by a mismatch between the optical powers of the eye and its axial length. More recently, myopia has emerged as an epidemic, most notably in urban East Asia.¹⁻³ The public importance of myopia as a health issue may be commonly underestimated because of the ease with which low levels can be treated with glasses, contact lenses and, more recently, refractive surgery. However, person with high myopia (≤ -6 D) are at a greater risk of chorioretinal disease.^{4,5}

Recently, retrospective association studies have reported an inverse relationship between the development of school-aged myopia and outdoor activity or sports,⁶⁻¹² with Jones et al.⁸ reporting that lower levels of sport or outdoor activity and having myopic parents, were the strongest nonocular predictors of the development of school myopia. More recently, findings from the Sydney Myopia Study have indicated that time spent outdoors during childhood, rather than outdoor activity (e.g., sports) per se, is a potent protective factor against the development of myopia. The authors have reported that children who spent a greater amount of time outdoors had a less myopic and more hyperopic mean refraction, whereas those students who combined high levels of near work with low levels of outdoor activity showed the least hyperopic refraction.⁷ One possible reason postulated to explain this protective effect is the higher ambient illuminance experienced outdoors. Supporting this postulate, a study of 71 myopic children with single-vision lens or bifocal correction reported that myopia progression rates were slower during the 6-month period that included summer vacation, when ambient illumination levels are higher, than during the winter.¹³

Recently, we have shown that exposing chicks to high illuminances, either sunlight ($\sim 30,000$ lux) or intense laboratory lights (15,000 lux), retards the development of deprivation myopia, compared to rearing chicks under normal laboratory illumination (500 lux).¹⁴

This finding raises two important questions: (1) Is the effect of light specific for deprivation myopia, or does it exert more general effects on the rate of emmetropization or its set point? (2) Since dopamine is one of the retinal neuromodulators with light-regulated release¹⁵⁻¹⁹ and also represents a known inhibitor of ocular growth,²⁰⁻²² could it be that the suppressive effects on deprivation myopia are mediated by dopamine? Rose et al.⁷ have hypothesized that changes in dopamine levels may explain the protective effect of time outdoors.

These questions were examined by treating chicks with spectacle lenses at high and normal laboratory illuminances, while using the administration of the dopamine D_2 antagonist spiperone to investigate whether dopamine is involved in the suppressive effect of light on deprivation myopia.

METHODS

Animal Housing

One-day-old male white leghorn chickens were obtained from a local hatchery in Kirchberg, Germany. The chickens were maintained in

temperature-controlled rooms in a 12–12-hour light–dark cycle, with incandescent illumination of 500 lux during the light phase, with lights on at 7 AM and off at 7 PM. They had unrestricted access to food and water and were given 7 days to become accustomed to their surroundings before the commencement of experiments. All experiments conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the university committee for experiments involving animals.

Experimental Design

Experiment A. Chicks were treated monocularly with either +7 or –7 D lenses, for 5 or 6 days, respectively. During the treatment period, the chicks were reared under either normal laboratory illuminance (500 lux, $n = 12$ for negative lenses, and $n = 16$ for positive lenses) or high ambient illuminance (15,000 lux, $n = 12$ or $n = 16$, respectively). For bright-light treatment, the chicks were exposed to 15,000 lux for a period of 5 hours per day (10 AM–3 PM) and were kept under an illuminance of 500 lux for the remaining period of the light phase. The lenses were cleaned daily during the process of refractive measurements.

Experiment B. Chicks were monocularly treated with diffusers for a period of 4 days, either under normal laboratory illuminance (500 lux, $n = 9$) or high ambient illuminance (15,000 lux, $n = 24$). Those treated under bright light received a daily intravitreal injection of either the dopaminergic antagonist spiperone (500 μ M, $n = 9$) or a vehicle solution (0.1% ascorbic acid, $n = 9$), with an untreated group serving as the control ($n = 6$). The chicks were exposed to the high illuminances for only 5 hours per day (10 AM–3 PM) and were kept under normal laboratory illuminance (500 lux) for the remaining period of the light phase.

On the day before treatment, the chicks were anesthetized by diethyl ether ventilation and had a Velcro ring glued to the feathers around the left eye. The right eye remained untouched and served as a contralateral control. For experiment A, either a –7 or +7 D lens was fitted to the left eye with a Velcro mount system. Lenses were cleaned daily (9:30 AM) after the measurements of refractive state. For experiment B, diffusers were attached as described elsewhere.²³

Measurement of Refractive State and Ocular Biometry

Refraction and axial length were measured by automated infrared photoretinoscopy^{23,24} and A-scan ultrasonography,²⁴ respectively.

Injection Protocol

With the chicks under light ether anesthesia, intravitreal injections were made daily with a handheld 30-gauge disposable syringe (MicroFine; BD Biosciences, Franklin Lakes, NJ) into diffuser-treated eyes just before the exposure to high illuminance. Intraocular injections consisted of 12.5 μ L of 500 μ M spiperone (Sigma-Aldrich, Munich, Germany) dissolved in a 1-mg/mL ascorbic acid solution (pH 7.4) or a vehicle solution (1 mg/mL ascorbic acid, pH 7.4), as appropriate. These doses were chosen on the basis of previous work, which showed a powerful effect on refractive development in chicks.²⁵

Light Sources

The light sources currently used have been described in detail.¹⁴ Briefly, the chicks were kept in an illuminance of 500 lux at cage level, as measured with a radiometer (IL1700 Research Radiometer; International Light, Inc., Newburyport, MA), under conventional ceiling-mounted fluorescent lights (400–800 nm, peaking at 530 and 620 nm, referred to as normal laboratory illuminance; Lumilux plus Triphosphor; Osram, Munich, Germany). For indoor high-illuminance experiments, the chicks were kept in specially designed cages with two 1500-W (230 V) quartz-halogen lights (300–1000 nm, peaking at 700 nm) situated 1.5 m above the cage. The lights provided an illuminance at cage level of roughly 15,000 lux. Air conditioning was necessary to

keep the temperature in the standard range (21°C). The viewing distance from the cage to the walls of the room was roughly 2.5 m and was unaffected by the mounting of the high-intensity lights above the cage.

Statistics

A multivariate analysis of variance (MANOVA), of repeated-measures design, was used to compare pre- and posttreatment values for the measured ocular parameters. A one-way ANOVA, followed by Student's unpaired *t*-test with Bonferroni correction for multiple testing, was used to analyze between-groups posttreatment values for measured ocular parameters. Results are presented as the mean \pm SEM.

RESULTS

Effects of Increased Ambient Illuminance on the Development of Myopia Induced by Negative Lenses

Chicks that were kept under an ambient illuminance of 500 lux rapidly compensated for the –7 D lenses, with full compensation almost reached by day 5 (change in refraction, -6.7 ± 0.5 D; Fig. 1, Table 1).

In contrast, chicks fitted with –7 D lenses and exposed to an ambient illumination of 15,000 lux for 5 hours per day showed a significantly slower rate of compensation, with full compensation not achieved until day 6 (change in refraction -7.0 ± 0.5 D; Fig. 1, Table 1). ANOVA testing, followed by a Student's *t*-test with Bonferroni correction, indicated a significant difference in refraction between the two light groups at days 3 ($P < 0.02$), 4 ($P < 0.03$), and 5 ($P < 0.01$). Axial length was measured only at the commencement, day 3, and the cessation of treatment. Axial lengths of negative-lens-treated eyes from chicks raised under an ambient illumination of 15,000 lux were significantly shorter than axial lengths of lens-treated eyes of chicks kept under 500 lux at day 3 (8.73 ± 0.08 mm vs. 8.92 ± 0.04 mm, $P = 0.02$), but, as expected, were not significantly different at the commencement or ces-

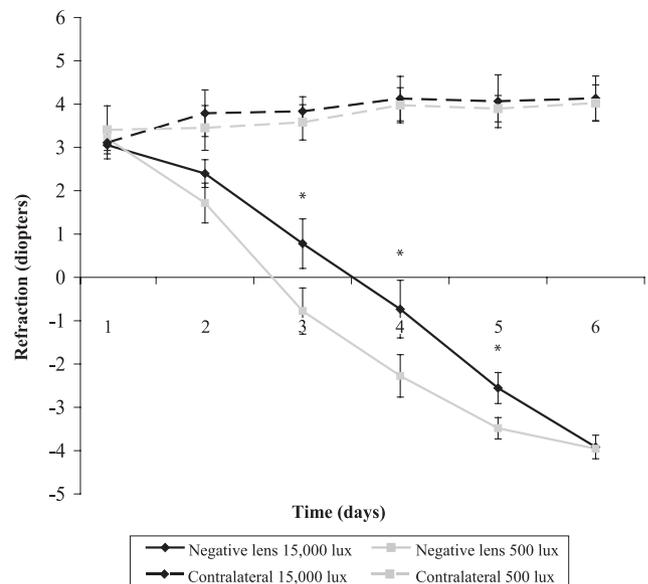


FIGURE 1. The effect of ambient illuminance on refractive development in chicks treated with negative lenses. Chicks were fitted with –7 D lenses over the left eyes and raised under either 500 lux ($n = 12$) or 15,000 lux ($n = 12$), for a period of 5 days. *Dashed lines*: refractive development of the fellow right eyes that remained unaffected by treatment. Error bars, SEM ($^*P < 0.05$).

TABLE 1. Effect of Ambient Illuminance on Ocular Parameters in Chicks Treated with Negative Lenses

	Refraction (D)					Anterior Chamber (mm)			Vitreous Chamber (mm)			Axial Length (mm)			
	D1	D2	D3	D4	D5	D6	D1	D3	D6	D1	D3	D6	D1	D3	D6
Negative lens, 500 lux	3.2 ± 0.2	1.7 ± 0.5	-0.8 ± 0.5	-2.3 ± 0.5	-3.5 ± 0.3	-4.0 ± 0.1	0.95 ± 0.03	0.98 ± 0.06	0.96 ± 0.04	5.02 ± 0.02	5.63 ± 0.04	5.65 ± 0.04	8.28 ± 0.02	8.92 ± 0.04	9.05 ± 0.05
Negative lens, 15,000 lux	3.1 ± 0.2	2.4 ± 0.3	0.8 ± 0.6	-0.7 ± 0.7	-2.6 ± 0.5	-3.9 ± 0.3	0.93 ± 0.04	0.95 ± 0.03	0.94 ± 0.06	5.05 ± 0.02	5.45 ± 0.03	5.62 ± 0.06	8.29 ± 0.02	8.73 ± 0.08	9.00 ± 0.05
Contralateral, 500 lux	3.4 ± 0.3	3.5 ± 0.3	3.6 ± 0.2	4.0 ± 0.2	3.9 ± 0.2	4.0 ± 0.2	0.94 ± 0.02	0.95 ± 0.03	0.94 ± 0.02	5.04 ± 0.03	5.17 ± 0.04	5.23 ± 0.04	8.29 ± 0.03	8.34 ± 0.03	8.53 ± 0.04
Contralateral, 15,000 lux	3.1 ± 0.1	3.8 ± 0.2	3.8 ± 0.2	4.1 ± 0.2	4.1 ± 0.3	4.1 ± 0.3	0.92 ± 0.02	0.94 ± 0.03	0.91 ± 0.02	5.02 ± 0.02	5.18 ± 0.06	5.26 ± 0.05	8.28 ± 0.04	8.31 ± 0.06	8.58 ± 0.06

sation of treatment ($P = 0.70$, $P = 0.52$, respectively). It should be noted, however, that the rate of axial elongation observed in this study in response to negative lenses, when compared with the rate of change in the axial length of contralateral control eyes, is significantly higher than normally reported in the literature.²⁶ This appears to be related to a lower rate of elongation in the contralateral control eyes than that normally observed. Changes in axial length represented changes in vitreous chamber depth ($y = 0.80x - 1.63$, $r^2 = 0.96$, Table 1), rather than alteration in anterior chamber depth (Table 1). Refraction ($F = 2.28$, $P = 0.17$) and axial length ($F = 3.93$, $P = 0.10$) of the contralateral eyes, exposed to normal vision, were unaffected by the treatment regimens, although, as mentioned, the rate of axial elongation was slower than that normally seen over the first 3 days of treatment.

MANOVA testing indicated a significant effect of lens treatment and light intensity, over time, on refractive development ($F = 539.5$, $P < 0.0001$; $F = 7.44$, $P = 0.03$, respectively) and axial length ($F = 63.1$, $P < 0.0001$; $F = 12.2$, $P = 0.008$, respectively). There was no significant difference in initial refractions ($F = 0.88$, $P = 0.35$) or axial lengths ($F = 0.03$, $P = 0.95$) between all treatment groups.

Effects of Increased Ambient Illumination on the Development of Hyperopia Induced by Positive Lenses

Unlike in negative lens wear, the rate of compensation for plus lenses was significantly enhanced by exposure to high ambient illuminance, with chicks reared under 15,000 lux showing almost full compensation as early as day 3 of treatment (change in refraction: $+5.3 \pm 0.6$ D), whereas chicks reared under 500 lux did not show similar amounts of compensation until day 5 ($+5.5 \pm 0.6$ D; Fig. 2). Analysis of variance, followed by a Student's *t*-test with Bonferroni correction, indicated a significant difference in the refraction of lens-treated eyes of the low- and high-illuminance groups at days 2 ($F = 6.1$, $P = 0.02$), 3 ($F = 9.1$, $P = 0.005$) and 4 ($F = 13.9$, $P = 0.001$).

There was no significant difference in axial length between the lens-treated chicks exposed to high or low illumination at either the commencement or cessation of treatment ($F = 1.26$, $P = 0.28$; $F = 1.54$, $P = 0.24$). However, consistent with the refraction results, there was a significant difference at day 3 of treatment ($F = 5.7$, $P = 0.01$; Table 2), which accounted for

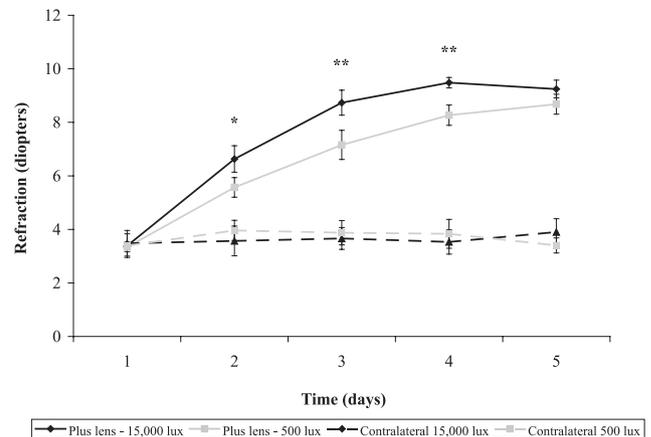


FIGURE 2. The effect of ambient illumination on refractive development in chicks treated with plus lenses. Chicks were fitted with +7 D lenses over the left eyes and raised under the light regimens shown in Figure 1. Dashed lines: refractive development of the fellow right eyes that remained unaffected by treatment. Error bars, SEM (* $P < 0.05$, ** $P < 0.01$); $n = 16$ per treatment group.

TABLE 2. Effect of Ambient Illuminance on Ocular Parameters in Chicks Treated with Plus Lenses

	Refraction (D)					Anterior Chamber (mm)					Vitreous Chamber (mm)					Axial Length (mm)				
	D1	D2	D3	D4	D5	D1	D3	D6	D1	D3	D6	D1	D3	D6	D1	D3	D6	D1	D3	D6
Plus lens, 500 lux	3.3 ± 0.2	5.6 ± 0.4	7.2 ± 0.5	8.3 ± 0.4	8.8 ± 0.4	0.95 ± 0.03	1.09 ± 0.02	1.06 ± 0.03	4.99 ± 0.02	5.13 ± 0.05	5.15 ± 0.03	8.26 ± 0.03	8.48 ± 0.04	8.47 ± 0.03						
Plus lens, 15,000 lux	3.4 ± 0.1	6.6 ± 0.5	8.7 ± 0.5	9.5 ± 0.2	9.3 ± 0.3	0.96 ± 0.02	1.02 ± 0.04	1.01 ± 0.04	4.97 ± 0.02	5.02 ± 0.02	5.09 ± 0.06	8.31 ± 0.05	8.32 ± 0.03	8.40 ± 0.04						
Contralateral, 500 lux	3.4 ± 0.2	4.0 ± 0.2	3.9 ± 0.1	3.8 ± 0.2	3.4 ± 0.2	0.93 ± 0.03	1.08 ± 0.03	1.07 ± 0.04	4.98 ± 0.03	5.23 ± 0.04	5.28 ± 0.04	8.31 ± 0.04	8.59 ± 0.03	8.60 ± 0.03						
Contralateral, 15,000 lux	3.5 ± 0.2	3.6 ± 0.1	3.7 ± 0.2	3.5 ± 0.2	3.9 ± 0.1	0.95 ± 0.03	1.09 ± 0.01	1.03 ± 0.03	5.00 ± 0.02	5.27 ± 0.03	5.29 ± 0.03	8.30 ± 0.05	8.58 ± 0.02	8.59 ± 0.02						

the changes in refraction. Changes in axial length represented changes in vitreous chamber depth ($y = 0.95x - 3.04$, $r^2 = 0.59$; Table 2), rather than alterations in the depth of the anterior chamber (Table 2). Refraction ($F = 1.09$, $P = 0.35$) and axial length ($F = 3.18$, $P = 0.12$) of the contralateral control eyes were unaffected by the treatment regimens.

MANOVA testing indicated that lens treatment and light intensity had a significant effect on refraction ($F = 101.7$, $P < 0.0001$; $F = 5.23$, $P = 0.02$) and axial length ($F = 25.6$, $P = 0.0001$; $F = 11.9$, $P = 0.001$), respectively, over time. There was no significant difference in the initial refractions ($F = 0.30$, $P = 0.82$) or axial lengths ($F = 0.46$, $P = 0.71$) between the treatment groups.

Effects of a Dopamine Antagonist on the Protective Effects of Light in Deprivation Myopia

Four days of diffuser wear, under 500 lux, induced significant amounts of myopia, in comparison to that in contralateral control eyes (Fig. 3; -9.1 ± 1.0 D vs. $+3.2 \pm 0.2$ D, $P < 0.0001$). Myopia development, however, was significantly retarded if chicks were exposed to 15,000 lux (-4.0 ± 1.1 D, $P = 0.01$). This retardation was unaffected by the daily intravitreal injection of a vehicle solution (-3.7 ± 0.6 D, $P = 0.8$). In contrast, daily injection of spiperone abolished the protective effect of high illuminances on deprivation myopia, with these chicks developing levels of myopia similar to those in the chicks that wore diffusers under an illumination of 500 lux (-7.8 ± 1.0 D, $P = 0.23$).

Changes in axial length reflected changes in refraction, with those chicks that wore diffusers under 500 lux and those chicks that were injected daily with spiperone and kept under an illumination of 15,000 lux developing the longest eyes (8.99 ± 0.06 and 9.00 ± 0.05 mm, respectively). In contrast, chicks kept under an illumination of 15,000 lux and injected with a vehicle solution had axial length (8.82 ± 0.06 mm) similar to that of chicks that were not injected at all (8.83 ± 0.03 mm; Table 3). Refraction ($F = 1.67$, $P = 0.20$) and axial length ($F = 1.40$, $P = 0.28$) of the untreated fellow eyes were unaffected by any treatment regimen.

A repeated-measures multivariate analysis of variance (MANOVA) indicated a significant effect of diffuser treatment and light intensity, over time, on refractive development ($F =$

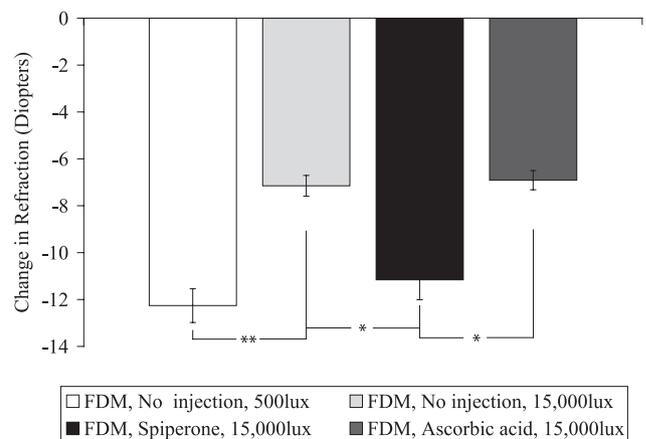


FIGURE 3. Changes in refraction over a 4-day period induced by ambient illuminance levels and spiperone in chicks fitted with translucent diffusers. The chicks were treated in one of four conditions for a period of 4 days: (1) ambient illumination of 500 lux, (2) ambient illumination of 15,000 lux, (3) ambient illumination of 15,000 lux, daily injections of spiperone, (4) ambient illumination of 15,000 lux, daily injection of a vehicle solution (1 mg/mL ascorbic acid). Error bars, SEM (* $P < 0.05$, ** $P < 0.01$).

TABLE 3. Effects of Ambient Illumination and Spiperone on Ocular Development of Chicks Fitted with Translucent Diffusers for a Period of 4 Days

Treatment	II (lux)	Refraction (D)		Anterior Chamber (mm)		Vitreous Chamber (mm)		Axial Length (mm)	
		Day 0	Day 4	Day 0	Day 4	Day 0	Day 4	Day 0	Day 4
		Constant diffuser	500	3.1 ± 0.3	-9.1 ± 1.0	1.05 ± 0.02	1.02 ± 0.03	4.96 ± 0.05	5.53 ± 0.06
Constant diffuser	15,000	3.2 ± 0.1	-4.0 ± 1.1	0.99 ± 0.03	1.02 ± 0.04	4.95 ± 0.04	5.39 ± 0.04	8.30 ± 0.04	8.82 ± 0.06
Constant diffuser, ascorbic acid	15,000	3.2 ± 0.2	-3.7 ± 0.6	1.02 ± 0.03	1.05 ± 0.03	4.99 ± 0.05	5.41 ± 0.04	8.30 ± 0.06	8.83 ± 0.03
Constant diffuser, spiperone	15,000	3.4 ± 0.1	-7.8 ± 1.0	1.03 ± 0.03	1.07 ± 0.03	4.97 ± 0.06	5.57 ± 0.06	8.34 ± 0.05	9.00 ± 0.05
Contralateral, constant diffuser	500	3.3 ± 0.3	3.2 ± 0.2	1.00 ± 0.03	1.05 ± 0.04	4.95 ± 0.05	5.24 ± 0.08	8.29 ± 0.05	8.60 ± 0.03
Contralateral, constant diffuser	15,000	3.2 ± 0.1	4.0 ± 0.3	0.99 ± 0.03	1.04 ± 0.03	4.95 ± 0.04	5.26 ± 0.05	8.31 ± 0.05	8.60 ± 0.04
Contralateral, ascorbic acid	15,000	3.0 ± 0.2	3.7 ± 0.2	1.00 ± 0.03	0.99 ± 0.03	4.99 ± 0.06	5.21 ± 0.04	8.33 ± 0.05	8.50 ± 0.02
Contralateral, spiperone	15,000	3.4 ± 0.1	4.2 ± 0.4	1.04 ± 0.02	1.02 ± 0.03	5.00 ± 0.06	5.21 ± 0.03	8.35 ± 0.06	8.53 ± 0.03

212.6, $P < 0.0001$; $F = 8.56$, $P = 0.007$; respectively) and axial length ($F = 9.9$, $P = 0.001$; $F = 4.2$, $P = 0.04$). There was no significant difference in initial refraction ($F = 0.46$, $P = 0.85$) or axial length ($F = 0.93$, $P = 0.49$), between all treatment groups.

DISCUSSION

We found that exposure to high ambient illuminance (15,000 lux) for 5 hours a day slowed compensation for negative lenses and accelerated compensation for positive lenses in chicks. End-point refractions, reflecting the set point of emmetropization, were not changed. Changes in refractions were consistently reflected in changes in axial length, indicating that all induced refractive errors were axial. Second, we found that the protective effect of bright light on deprivation myopia could be abolished by intravitreal administration of a D₂ dopaminergic antagonist, spiperone.

Pupil Size and Depth of Focus

A possible interaction that should be considered is the change of pupil size in bright light. Schaeffel et al.²⁷ found that the pupil size in chicks is reduced by roughly 50% of its maximum diameter under an illuminance of only 1000 lux. It is clear that a smaller pupil size increases the depth of focus and may therefore diminish the error signal driving emmetropization. However, changes in depth of focus cannot explain why bright light accelerated compensation for positive lenses. Furthermore, the development of deprivation myopia was also significantly suppressed under bright light, even though depth of focus does not play a role under the diffusers. In summary, changes in depth of focus cannot explain the effects of high illuminance on compensation for imposed defocus. Pupil constriction apparently also has no effect on refractive development in the uncovered fellow eyes.

Effect of Enhanced Locomotor Activity on Optic Flow

Another possibility is that chicks show elevated levels of physical activity under high ambient illumination, creating greater optic flow and hence faster local luminance changes on the retina. Rapid luminance changes were previously proposed to inhibit myopia's development²⁸; however, we have shown that there is no difference in the activity of chicks exposed to 15 minutes of diffuser-free vision under either high or normal ambient illumination.¹⁴

Effects of Bright Light on Retinal Dopamine

A possible link between light and myopia development is the neurotransmitter dopamine, whose release from the dopaminergic amacrine cells is light sensitive.¹⁵⁻¹⁹ Dopamine (DA) is localized to a subpopulation of amacrine cells, with D₂ receptors implicated in myopia development.²¹ These receptors are localized to the basal layer of the retinal pigment epithelium, inner segment of the photoreceptor cells, inner nuclear layer, inner plexiform layer, and autoreceptors on the dopaminergic cells.^{29,30} DA has long been postulated to play a critical role in the regulation of ocular growth, with the diurnal release of DA in chicks and monkeys disrupted during the development of deprivation myopia.^{31,32} Weiss and Schaeffel³² observed a 30% reduction in daytime retinal DA levels during the development of deprivation myopia. Further, the intravitreal injection of DA agonists such as apomorphine,^{20-22,33} 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (ADTN),^{25,34} and quinpirole²⁵ retards the development of FDM and lens-induced

myopia, implying a role for DA in the modulation of eye growth.

We found that the protective effect of bright light on development of deprivation myopia can be abolished by the daily intravitreal injection of the specific D₂ receptor antagonist spiperone. This finding suggests that the protective effect of light against the development of deprivation-myopia is mediated by dopamine. In support, McCarthy et al.²⁵ have reported that the ability of brief periods of normal vision to retard the development of deprivation-myopia can be blocked by the prior intravitreal injection of spiperone. Similarly, if the chicks were placed in the dark during the period of diffuser removal, the protective effect seen when the diffusers were removed in the light was lost; however, this protective effect could be restored if a DA agonist was injected before dark exposure.²⁵ These findings support the idea that the ability of brief periods of normal vision to retard the development of deprivation myopia is partially driven by changes in DA signaling.

Although spiperone is a high-affinity D₂ receptor antagonist,^{35,36} it also binds to the serotonin (5-HT) receptor 5-HT_{2A} and adrenoceptor α_{1A} , with considerable affinity^{37,38} and to a lesser extent to the serotonin receptor 5-HT_{1A} and the adrenoceptor α_{1B} .^{37,38} Serotonin has been localized within the avian retina to a subset of amacrine cell bodies in the inner nuclear layer, with their distal dendrites stratified at the inner margin of the inner plexiform layer.^{39,40} More recently, a role for serotonin in the regulation of eye growth has been postulated based on the findings that 5-HT antagonists retard the development of lens-induced myopia, but surprisingly have no effect on deprivation myopia.⁴¹ Reserpine, which depletes both serotonin and dopamine vesicle stores, suppresses both lens-induced myopia and deprivation-myopia.⁴² There are no studies published in which a role has been investigated for epinephrine or norepinephrine in the regulation of ocular growth.

Whether retinal dopamine content and release can determine the rate of the compensation for negative lenses is a central question that requires further study. In particular, the dose-response function of bright light on the suppression of myopia has to be determined, and it has to be shown that dopamine content and release are still enhanced after 2 days of daily exposure of bright light, when the inhibitory effect on myopia is maximal.

The role of dopamine in the acceleration of the compensation for defocus imposed by positive lenses is less clear. Although it may be that the higher rate of compensation is set by higher dopamine levels, in other studies, a downregulation or little change has been observed in the expression in vitreal DOPAC levels in response to plus-lens wear⁴³ although Guo et al.⁴⁴ have reported an upregulation in retinal DOPAC levels. Further, Schmid and Wildsoet²² have reported that administration of a dopamine agonist, apomorphine, does not alter compensation for positive lenses. However, the speed of the response, important for the question raised herein, was not studied.

There are several other possible explanations for the negative correlation between outdoor activity and the incidence of myopia that have been discussed in another publication.⁷ They include the lack of peripherally imposed hyperopic defocus outdoors with longer viewing distances (assumed to be a factor driving myopia during reading),⁴⁵ the lack of accommodation, and the resulting lag in accommodation that may also impose hyperopic defocus.

IMPLICATIONS AND CONCLUSIONS

Exposure to high illuminance levels reduces the rate of ocular growth normally seen in response to the fitting of negative

lenses or translucent diffusers, and enhances the growth suppression of plus lenses, but does not alter normal ocular development. Further, the protective effect of light against the development of myopia appears to be mediated by dopamine, as the injection of a dopamine D₂-specific antagonist abolishes the protective effect of light, at least in the case of deprivation myopia.

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