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What Do Animal Studies Tell Us about the Mechanism of Myopia – Protection by Light?

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Abstract

Human studies have provided strong evidence that exposure to time outdoors is protective against the onset of myopia. A causal factor may be that the light levels outdoors (30,000 – 130,000 lux) are much higher than light levels indoors (typically less than 500 lux). Studies using animal models have found that normal animals exposed to low illuminance levels (50 lux) can develop myopia. The myopia and axial elongation, produced in animals by monocular form deprivation, is reduced by light levels in the 15,000–25,000 range. Myopia induced with a negative-power lens seems less affected, perhaps because the lens provides a powerful target for the emmetropization mechanism. Animal studies suggest that raising the light levels may have their effect by increasing retinal dopamine activity, probably via the D2 receptor pathway, altering gene expression in the retina and reducing the signals that produce axial elongation.

Keywords

myopia; animal models; light levels

As described in the previous papers that discussed the question “Do human studies ‘prove’ that (i) outdoor activity is protective, (ii) light is the agent,” human studies[1–7] have provided strong evidence that exposure to time outdoors is protective against the onset of myopia and suggest that it is the light levels outdoors that are the causal factor. Animal models are helping us to discover how and why outdoor activity is effective and if, indeed, the causative agent is the higher light levels experienced outdoors. It is important to note that terms like “high” or “bright” or “elevated” light levels refer to the illuminance levels (measured in lux) relative to indoor lighting, which is typically 500 lux or less. Most diurnal terrestrial creatures, including humans, evolved outdoors where light levels are much higher. Illuminance on a sunny day exceeds 100,000 lux. Even on a cloudy day, levels of 10,000 to 20,000 lux are typical. Thus, the “elevated” light levels shown to be protective in animal studies (10,000 – 40,000 lux) are actually lower than those usually encountered outdoors.

Using animal models, we can examine the effect of illuminance levels both on normal refractive development and on the response to myopiagenic stimuli. During normal

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refractive development, the illuminance level has a very powerful effect. Cohen et al.[8] showed that chicks raised in cages with 10,000 lux on a 12hr/12 hr light-dark cycle emmetropize normally. Like most animals and humans, they initially are hyperopic. Then, over the first weeks after hatching, the hyperopia declined toward emmetropia, but stabilized at around 1.1 diopters (D) of hyperopia – a level that is easily cleared with a small amount of accommodation. Chicks raised in 500 lux, also emmetropized, but by 90 days of age the mean refraction was 0.03 D and some animals were slightly myopic. Animals raised in 50 lux initially emmetropized, but then all of the animals progressed below emmetropia and became myopic (average at 90 days, −2.4 D). One can look at this study two ways: on the one hand it says that "elevated" illuminance (10,000 lux) is protective against spontaneous myopia compared with standard (500 lux) illuminance. On the other hand, it says that low illuminance (50 lux) can produce myopia even without the presence of known myopiagenic stimuli.

At a similar early stage in refractive development, the wavelength of the ambient light also can have a powerful effect. As reported at the 15th International Myopia Conference in Wenzhou, China tree shrews exposed to steady or flickering long-wavelength (red) light, that only stimulates the long-wavelength sensitive (LWS) cones, slow the rate of axial elongation so that the eyes remain strongly hyperopic.[9] Interestingly, this occurs with as little as 2 hours per day of red exposure (the rest of the 14 hour day in fluorescent colony lighting).[10] Full-time exposure to red also produces hyperopia in older, adolescent tree shrews that have completed emmetropization.[11]

Most animals do not develop myopia spontaneously. Myopia is induced by placing a diffuser (form deprivation, FD) or a negative-lens over an eye for a period of days or weeks. Both cause the affected eye to increase its axial length (vitreous chamber depth), moving the retina behind the normal focal plane. Exposure to elevated illuminance while animals are in these myopiagenic conditions can reduce the rate at which of induced myopia develops compared to the myopia that develops in colony lighting (typically under 500 lux). The myopia in monocularly FD chicks, monkeys and tree shrews over a limited period of time (days, weeks) is reduced by light levels in the range of 10,000 – 40,000 lux.[12–14] Interestingly, elevated light (below 40,000 lux) did not reduce the *incidence* of FDM in chicks and tree shrews – all animals developed some myopia. However, illuminance of about 25,000 lux did reduce the incidence (prevent myopia from developing) in some macaque monkeys[13] and illuminance of 40,000 prevented myopia incidence in chicks. In contrast, myopia induced by negative lens wear was not blocked in monkeys, tree shrews, or chicks[14–16] although the rate of development was slowed. Given enough time, the lens-wearing eyes fully compensated for the negative lens so that the lens-wearing eye was emmetropic (the refraction, measured with the lens in place, matched the refraction of the control eye). With the lens removed, the treated eyes were myopic.

The difference between the response to FD and negative lens wear may underscore an important difference between these two myopiagenic stimuli. FD removes the possibility of achieving clear images on the retina, placing the emmetropization mechanism in an "open loop" condition where light levels may be better able to affect the generation of retinal GO and STOP signals. In contrast, a negative lens provides a "target." When first applied, it

moves the focal plane behind the retina, producing refractive hyperopia. As the eye elongates, the hyperopia lessens and dissipates completely when the eye has elongated to the point where the retina has moved to the shifted focal plane.

Which stimulus is a better model for the environmental conditions that produce human myopia? In most children, there is no form deprivation. However, to the extent that hyperopic defocus, caused by underaccommodation to near targets, is a stimulus for axial elongation, (the blur hypothesis.[17]) there is also no fixed "target", similar to the situation with FD. This is because, as the eye elongates in response to the hyperopic defocus, the underaccommodation continues so that there is continued hyperopic defocus. In that sense, (and only in that sense) it is similar to form deprivation. To the extent that the lack of a fixed target is an important factor in the effectiveness of high illuminance in slowing myopia, the more consistent effects of high illuminance on slowing myopia in response to FD in animals may suggest that additional studies in children exposed to outdoor activity will find at least a small slowing of myopia progression.

Animal models are also helping us to make major inroads into the retinal mechanisms by which light levels can modulate axial elongation and refractive state and the response to myopiagenic stimuli. Many neurotransmitters and peptides in the retina have been implicated in generating the retinal signals that increase axial length ("GO" signals) or retard axial elongation ("STOP" signals).[18–22] One of these is dopamine, a neurotransmitter used by a class of amacrine cells.[23–29] Increased release of dopamine may slow elongation and decreased levels may facilitate elongation.[14,30,31] The interest in dopamine in relationship with illuminance is that increasing light levels produce increased dopamine activity. Indeed, if the illuminance is increased to 40,000 lux, the progression of myopia in FD chicks is arrested.[32] Moreover, if the dopamine D2 receptor antagonist spiperone is administered intravitreally in chicks exposed to high illuminance, the protective effect of the light is removed.[16] In conclusion, studies in animals models have provided evidence that "high" illuminance facilitates normal emmetropization, that levels of 10,000 lux or more can slow the progression of induced myopia and that retinal dopamine may play a critical role in these effects.

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