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Research article

Brief light exposure at night disrupts the circadian rhythms in eye growth and choroidal thickness in chicks

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ABSTRACT

Changes in ocular growth that lead to myopia or hyperopia are associated with alterations in the circadian rhythms in eye growth, choroidal thickness and intraocular pressure in animal models of emmetropization. Recent studies have shown that light at night has deleterious effects on human health, acting via "circadian disruptions" of various diurnal rhythms, including changes in phase or amplitude. The purpose of this study was to determine the effects of brief, 2-h episodes of light in the middle of the night on the rhythms in axial length and choroidal thickness, and whether these alter eye growth and refractive error in the chick model of myopia.

Starting at 2 weeks of age, birds received 2 h of light between 12:00 am and 2:00 am for 7 days (n = 12; total hours of light: 14 h). Age-matched controls had a continuous dark night (n = 14; 14L/10D). Ocular dimensions were measured using high-frequency A-scan ultrasonography on the first day of the experiment, and again on day 7, at 6-h intervals, starting at noon (12 pm, 6 pm, 12 am, 6 am, 12 pm). Measurements during the night were done under a photographic safe-light. These data were used to determine rhythm parameters of phase and amplitude. 2 groups of birds, both experimental (light at night) and control, were measured with ultrasound at various intervals over the course of 4 weeks to determine growth rates. Refractive errors were measured in 6 experimental and 6 control birds at the end of 2 weeks.

Eyes of birds in a normal L/D cycle showed sinusoidal 24-h period diurnal rhythms in axial length and choroid thickness. Light in the middle of the night caused changes in both the rhythms in axial length and choroidal thickness, such that neither could be fit to a sine function having a period of 24 h. Light caused an acute, transient stimulation in ocular growth rate in the subsequent 6-h period (12 am–6 am), that may be responsible for the increased growth rate seen 4 weeks later, and the more myopic refractive error. It also abolished the increase in choroidal thickness that normally occurs between 6 pm and 12 am.

We conclude that light at night alters the rhythms in axial length and choroidal thickness in an animal model of eye growth, and that these circadian disruptions might lead to the development of ametropias. These results have implications for the use of light during the night in children.

1. Introduction

Until the advent of artificial lighting over the past 2–3 centuries, life was adapted to daily 24-h cycles of darkness and light, and animals (including man) have developed endogenous circadian rhythms synchronized to this cycle, to optimize survival strategies. The modern use of artificial light indoors during both day and night has permanently altered the natural lighting cycle. The negative impact of the increasing prevalence of nighttime illumination resulting from city lights and modern conveniences such as luminous signs on the night environment (Cinzano et al., 2001) and nocturnal species may extend to the realm of human health concerns (Chepesiuk, 2009; Stevens et al., 2013). For instance, bedroom night-lights were associated with the development of myopia in children (Quinn et al., 1999) (however this remains controversial as two subsequent studies found no such association (Gwiazda et al., 2000; Zadnik et al., 2000). Scientific studies have recently linked light at night to increased risk for cancers (review: (Feillet et al., 2015), metabolic changes leading to obesity, mood disorders and cardiovascular disease (Chepesiuk, 2009; Anisimov et al., 2012;

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Stevens et al., 2013). Even dim light at night, for instance, from computer screens or televisions, can adversely affect the rhythm in melatonin, a hormone that influences sleep and daily rhythms of physiology, which then leads to alternations in the rhythms in loco–motor activity and core body temperature (Fonken et al., 2013; Borniger et al., 2014). The physiological basis of these adverse effects is the impingement of light on the clock driving endogenous rhythms (Wyse et al., 2011; Anisimov et al., 2012). It is well established that brief periods of light at certain times of night (dark part of the L/D cycle) have effects on the phases of circadian systems; these effects are generally most robust when close to dawn (lights on) or dusk (lights off), causing phase advances and delays, respectively. However, light in the middle of the night can also affect the clock, and cause a dampening of the rhythm amplitude, and/or acute affects.

Circadian disturbances, including phase shifts and effects on circadian clock outputs (e.g., melatonin or dopamine) (Stevens et al., 2013) may have profound effects on refractive development. This was first shown in chickens that were reared under constant light conditions: eyes grew excessively long and the corneas flattened (Lauber et al., 1961; Lauber and McGinnis, 1966; Li et al., 1995). Constant darkness too, caused excessive eye growth (Gottlieb et al., 1987). The resulting ametropias (refractive errors) depended on the length of time in the abnormal lighting condition, but it was undisputable that eye growth was altered. In chickens (Weiss and Schaeffel, 1993; Nickla et al., 1998a; Papastergiou et al., 1998) as well as in primates (Nickla et al., 2002) including humans (Stone et al., 2004; Wilson et al., 2006; Chakraborty et al., 2011), the length of the eye oscillates in a diurnal manner, increasing in length during the day and stopping growth, or even decreasing in length, at night. The thickness of the choroid also shows a diurnal rhythm, the phase of which is opposite that of eye length: choroids thicken at night and thin during the day (Nickla et al., 1998a; Brown et al., 2009; Chakraborty et al., 2011). It has been found that circadian disruptions in these rhythms are associated with alterations in ocular growth patterns and refractive development: their phases and/or amplitudes are altered in eyes growing too fast, in response to form deprivation (no image) or negative lens-induced hyperopic defocus (image focused behind the retina), or too slowly, in response to positive lens-induced myopic defocus (image focused in front of the retina) (Nickla et al., 1998a; Papastergiou et al., 1998; Nickla, 2006). In all of these previous experiments documenting the effects of abnormal visual conditions on eye growth, eyes were continuously exposed to the visual condition, which could be argued does not approximate the common visual experience of children, whose nighttime exposure to light would likely not be continuous, but rather for relatively brief periods. With this in mind, we examined the effects of 2 h of light exposure, in the middle of the night, on the circadian rhythms in axial length and choroid thickness, and on eye growth rate, in young chicks. We report that light at night disrupts the sinusoidal diurnal rhythms in axial length and choroidal thickness. Parts of this manuscript have been presented in abstract form (Nickla and Totonelly, 2013).

2. Methods

2.1. Subjects

White Leghorn chicks (*Gallus gallus domesticus*) were hatched in an incubator and raised from day one in temperature – controlled brooders. The light cycle was 14L/10D; the light level in the brooders was about 500 lux. Food and water were supplied *ad libitum*. Care and use of the animals conformed to the ARVO Resolution for the Care and Use of Animals in Research.

2.2. Paradigm

2.2.1. Diurnal rhythms in axial length and choroidal thickness

Starting at 12-days of age, birds received 2 h of light (700 lux) between 12:00 am and 2:00 am for 7 days (n = 12; only one eye was used in data analyses). The "daytime" (period of light) was changed from 14 h to 12 h, from 7:30 am to 7:30 pm, which together with the 2 h of light at midnight totaled 14 h of light and 10 h of dark, as in the previous 2 weeks of life. Chicks were put into temperature controlled light-tight chambers at 7:30 pm, immediately before the time of "lights off"; the timer was set to turn the light on for the 2-h interval, then off. Two groups of birds comprise these data. The first (n = 6) were otherwise untreated except for the light regimen; only the right eyes were used in the data analysis. The second (n = 6) wore monocular −10 D lenses for 10 out of the 12 h of light during the day (i.e. lenses were NOT worn during the 2 h of light at night); the fellow untreated left eyes (*not* wearing lenses) comprise the second group of experimental eyes, for a total of 12 eyes: 6 right and 6 left. 2-way ANOVAs comparing the two data sets as a function of time showed no significant differences ($p > 0.1$) so these data were combined.[1] However, in the interest of diligence and accuracy, data and the statistical analyses are reported for both the combined data ("Full data set") as well as for only the 6 eyes of the six otherwise untreated birds ("Subset"). Controls were age-matched birds that received no light at night ("dark night") on a 14L/10D cycle, with lights turned on at 7:30 am and off at 9:30 pm (n = 14); only the right eye for each bird was used in the analyses. Two experiments make up these control data.

Ocular dimensions were measured using high-frequency A-scan ultrasonography at noon at the start of the experiment, under inhalation anesthesia (for details see Nickla et al., 1998a). On day 7 of the experiment, eyes were re-measured with ultrasound at 12 pm, 6 pm, 12 am, 6 am and 12 pm to obtain the parameters of the diurnal rhythms in axial length and choroidal thickness (see below). Measurements at night were done under a photographic safe light; measurements typically took about 5 min per eye, after which the birds were returned to the dark cage. Refractive errors were measured at the end of the experiment for a cohort of 6 experimental and 6 control birds (the same cohort for which "short term" growth rates were measured; below) using a Hartinger's refractometer.

2.3. Growth rate

Two separate sets of 12-day old birds were subjected to the same lighting protocols (2 h of light at night vs no light at night starting at age 12 days) and measured with ultrasound at various intervals to obtain detailed growth rate data. The "short term" set were measured using ultrasonography at noon on the first day (12 days of age), and then again at 24, 96, 120, 144 and 168 h later (n = 6 birds in each condition; only right eyes used) (Fig. 3A). The "long term" set were exposed to the lighting protocols (2 h of light at night vs no light at night starting at age 12 days) for 28 days, and were measured on day 1, day 7, day 21 and day 28 (control, n = 12 birds; experimental, n = 22 birds; only left eyes used).

[1] We justify the inclusion of these fellow eyes by the following: First, 10 out of 12 daily hours of minus lens-wear has a negligible effect on emmetropization (Schmid and Wildsoet, 1996) hence the likelihood of the lenses affecting the *fellow* eyes is negligible, especially as they were not worn during the night exposure. Second, there is no substantive effect on the sinusoidal nature of either rhythm by the wearing of negative lenses (Nickla, 2006), and finally, both rhythms in fellow eyes of monocular minus lens-wearing birds are normal, i.e. there is no evidence of "yoking" (unpublished data).