ORIGINAL ARTICLE

Pupillary Size and Light Reflex in Premature Infants

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ABSTRACT

The authors examined pupillary light reflexes to both red and blue stimuli using infrared video-pupillography in premature infants. Pupillary light reflexes were obtained in response to 470 nm blue and 635 nm red stimuli with varying intensities of 10 cd/m² and 100 cd/m². Red stimuli did not evoke a pupillary response in premature infants. However, blue stimuli produced a pupillary reflex, and the extent of the reaction was dependent on the intensity of the stimulus. These results suggest that in premature infants, the origin of light reflex may be mediated predominately by melanopsin-containing retinal ganglion cells.

Keywords: Infrared video-pupillography; light reflex; melanopsin; premature infants; pupil

INTRODUCTION

Pupil size in humans reaches a peak during the second decade after birth.¹ Studies have examined pupillary size and pupillary response using achromatic light stimuli during critical periods of visual development, especially in neonates and younger children.^{2–4}

The light reflex is mediated predominantly by cones and partially by rods, both of which are retinal photoreceptor cells. Melanopsin-containing retinal ganglion cells (mRGCs) can also induce a pupillary light reflex under strong blue light stimulation at 470 nm.^{5–7}

In this study, we examined the pupillary size and light reflex in premature infants using infrared video-pupillography and stimuli of red and blue light.

MATERIALS AND METHODS

Subjects

Subjects included 23 premature infants in the neonatal intensive care unit of Kitasato University Hospital. The mean gestational age was 32.2 ± 3.1 weeks (range:

28–35 weeks), and the mean birth weight was 1638 ± 643 g (range: 725–3554 g). The mean number of weeks at the time of measurement was 37.5 ± 1.4 weeks (range: 36–41 weeks). Subjects with poor general condition or retinopathy of prematurity were excluded. Children aged <10 years with good visual acuity and stereoscopic vision were also examined ($n=6$ for each year of age). We also examined six 20-year-old subjects in the same manner as the control subjects. None of the subjects had been administered medications that affect to the pupil.

This study was approved by the Kitasato University School of Medicine Ethics Committee (10-624). Informed consent was obtained from the parents or guardians of all subjects after having explained the objectives of the study.

Video-pupillography

An Iriscorder Dual C-10641 (Hamamatsu Photonics K.K.) remodelled for premature infants was used for recording the pupil size. With this device, stimulation with a 470 nm blue light or a 635 nm red light can be selected, and the luminance and duration can also be adjusted.⁸

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Each subject was placed under dark-adapted condition for 5 minutes, and the light reflex was measured under red light stimulation of 10 and 100 cd/m². Measurements were also obtained with blue light stimuli of 10 and 100 cd/m² intensities in the same manner. The duration of each procedure was 15 seconds in total: 2 seconds before, 5 seconds during, and 8 seconds after the light stimulation. The change in pupil size was also recorded simultaneously.

Examined Factors and Statistical Analysis

- (1) Initial pupil size (mm): pupil diameter before light stimulation.
- (2) Constriction amplitude (%): percentage of minimum pupil size during light stimulation in relation to the initial pupil diameter.

Constriction amplitude (%)

$$= \left[\frac{(\text{pupil diameter immediately before stimulation (mm)} - \text{minimum pupil size during stimulation (mm)})}{\text{pupil diameter immediately before stimulation (mm)}} \right] \times 100$$

The Scheffé test was used for statistical evaluation of differences between means. $p < 0.05$ was regarded as statistically significant.

RESULTS

Figure 1 shows the initial pupil size. The mean initial pupil size of the premature infants was significantly smaller than those of children >2 years old. Figure 2

FIGURE 1 Initial pupillary size by age. The initial pupil size of the 38-week premature infant was 3.9 mm, which is significantly smaller than that of children >2 years old. * $p < 0.05$.

shows the actual recordings of the light reflex of a 38-week-old premature infant using an infrared pupillometer. In all premature infant subjects, pupil constrictions were not induced under red light stimuli of either 10 or 100 cd/m². On the other hand, the pupil constriction amplitude under blue light stimuli was $21.9 \pm 6.1\%$ and $33.8 \pm 11.7\%$ when the luminance was changed from 10 to 100 cd/m², respectively, indicating that the pupil constriction amplitude was significantly higher with a higher luminance (Figure 3). Figure 3 also shows the pupil constriction amplitude based on age. In children >2 years old, the constriction amplitudes both under red and blue light stimuli did not significantly differ with normal adult subjects.

DISCUSSION

Several studies have examined the pupillary size of very immature infants.²⁻⁴ The usual pupillary size for these infants was shown to be less than 4 mm. In our study, the pupil size of 38-week-old premature infants was 3.9 mm in average, which was significantly smaller than the pupil size in children >2 years old. One reason for this finding is that the ocular and corneal diameters of premature infants are also smaller than those in children >2 years old.

The pupil light reflex has been reported to be absent in premature infants of <30 weeks gestational age, but developing gradually and is well developed by 35 weeks based on previous reported studies.^{2,4} Another study reported that a light response of 0.5 mm or more can be observed from at >31 weeks of age.⁴ The pupil of premature infants during this period does not respond usually to tyramine and hydroxyamphetamine hydrobromide, indicating that

FIGURE 2 The actual recording of the light reflex of a 38-week premature infant (10 cd/m²). Although, pupil constriction was not induced under red light stimuli, the pupil constriction amplitude under blue light stimuli was 27.7% in this case.

FIGURE 3 The pupil constriction amplitude by age. In all premature infant cases, pupil constriction was not induced under red light stimuli of both 10 and 100 cd/m². The constriction amplitude under blue light stimuli in premature infants was significantly smaller than that of children >2 years old. * $p < 0.05$.

the accumulation and release of norepinephrine at the neuromuscular junction is not fully developed.⁴ Moreover, Hanita et al. observed that at 33 weeks gestational age, the infant's pupil will not respond to a 600 nm single wavelength of light (5 μ W/cm²), which lies outside the range of perceptibility of melanopsin.⁹ However, the response of the infant's eye to white light (28 μ W/cm²) was similar to that of an adult, including wavelengths <590 nm, suggesting that the 33-week infant's pupillary light reflex was matured sufficiently to respond as that of an adult.

Our results also showed that the pupils of 38-week-old premature infants did not constrict under red light stimulation (635 nm). The pupils did constrict under blue light (470 nm) at both 10 and 100 cd/m² intensities. The 470 nm blue light used in this study stimulates not only the photoreceptor cells, but also mRGCs.^{5–8} In the report of Tarttelin et al. concerning the time of expression of opsin during early stages of development, melanopsin was present, but rhodopsin was not observed in human embryos at 8–13 weeks gestational age.¹⁰ Our present findings are consistent with those of Hanita et al. and Tarttelin et al.^{9,10}

Generally, vision can be classified into two types: image forming and non-image forming. Image forming is involved in the cognitive response to spatial objects through cone and rod cells. Non-image forming sets circadian clocks through retinal ganglion cells (RGCs) by 470 nm strong blue light and is involved in the light reflex. The production of melatonin is not fully developed in premature infants.¹¹ However, our results suggest that non-image-forming vision, which is a primitive biological function, begins to develop in the neonatal period. At 2 years old, the image-forming function is well developed through the aid of cone photoreceptors, which respond to red light

stimulation. These results suggest that in premature infants, the origin of the light reflex is mediated predominately by mRGCs. Therefore, the pupillary light reflex in premature infants must be measured using different intensities and wavelengths of light stimulation.

In conclusion, rods/cones appear unable to elicit a pupil reflex in preterm infants, although the mRGCs do respond to light at the correct wavelength for melanopsin. These results suggest that preterm babies do not have fully functioning retinas. Only the primitive non-image-forming system is operational, and the more sophisticated rod/cone system develops full functionality during later postnatal life.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Note: Figures 2 and 3 of this article are available in colour online at <http://informahealthcare.com/oph>.

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