Pupil response to melanopsin-containing retinal ganglion cells studied with a multi-primary illumination system

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Introduction: It is widely accepted that the constriction and dilation of the pupils is evoked by changes in the ambient luminance and it has been shown that signals in the cone-opponent mechanism also contribute to a pupillary control mechanism. These facts suggest that retinal rod-cone pathways strongly contribute to the pupillary control mechanism. A recent study has shown that retinal ganglion cells containing the photopigment melanopsin, which are intrinsically photosensitive in primates, project to the pupillary control center in the pretectum. The aim of this study was to investigate how signals driven by melanopsin-containing ganglion cells and by the other visual photoreceptors contribute to the pupillary control mechanism.

Methods: To independently stimulate the melanopsin-containing retinal ganglion cells from the other photoreceptors we designed and built a novel multi-primary stimulation system. The illumination system consists of an optical diffuser and an integrating sphere in which light-emitting diodes (LEDs) were used as internal light sources. Luminance output of each LED was controlled by pulse width modulation units by adjusting a duty cycle of pulse train. We calculated excitations of the melanopsin-containing ganglion cells and the other photoreceptors on the background and the test stimulus, expressed as a relative modulation between them. We used three test stimuli modulating luminance (LUM), modulating color (COL), and modulating an excitation of the melanopsin-containing ganglion cells (M-GC).

Results: The pupillary response evoked by LUM had a transient temporal property and the response evoked by COL had a sustained temporal property with a delay of ca. 60ms compared with that evoked by LUM. These results are consistent with previous results. The pupillary response evoked by M-GC had a sustained response compared with that evoked by LUM.

Conclusions: We made a multi-primary illumination system to independently stimulate melanopsin-containing ganglion cells. Our results indicated that the stimulus modulating excitation of the melanopsin-containing retinal ganglion cells evoked a large sustained pupillary response compared with that evoked by the luminance stimulus.

Pupillary light reflex in blind retinitis pigmentosa patients investigated before and after implantation of a subretinal visual prosthesis

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Objective: It has been regarded as a fact that blindness as a late stage of degenerative retinal diseases like retinitis pigmentosa (RP) is associated with a lack of common stimulus-response characteristics of the pupil light reflex or an absent light reaction. According to novel knowledge about the role of melanopsin ganglion cells for e.g. the pupillary light reflex this association may be put into question. In the course of the study recruitment for the first clinical pilot trial with a Subretinal Active Multiphotodiode Array (MPDA; RIM Pilot Trial; Princ. Inv. Prof. E. Zrenner) we investigated this matter systematically in blind RP patients. Pupillography was the objective part of a large test battery applied for safety and efficacy assessment in this trial.

Methods: CIP is an automated infrared video pupillograph (AMTech, Germany). We applied stimulus intensities of 0.36, 4.0, 36.3 lx (corneal illumination) in a dark room. The mean of the latency and amplitude of the PLR averaged from four complete and reliable pupillograms entered the analysis. The study design was open and prospective, however with a functional placebo-control keeping the subject and the examiner blind to the condition. The latter means that the power supply of the device was switched on/off by a third person according to a randomisation list. Therefore, each examination was performed twice (both conditions) at the respective visit.
All patients were suffering from RP, they were legally blind and had no reproducible light perception. Ten patients were tested during the pre-screening (baseline) at the Department of Ophthalmology. Eight of them were included in the RIM trial according to the in- and exclusion criteria, seven patients were implanted and controlled by pupillography after implantation and explantation of the device taking place 30 days later. All seven patients were men, aged 44, 48, 54, 52, 57, 27 and 53 years. The RIM study was approved by the local ethics committee and all subjects had given their written informed consent to participation.

Results: At baseline examination (n=10), no light reflex was elicitable for the lowest intensity stimulus condition of 0.36 lx; for 4.0 lx amplitude was 0.13 +/- 0.28; for the brightest stimulus intensity of 36.3 lx constriction amplitude was 0.47 +/- 0.4 mm. Surprisingly, we inconsistently noted that – in contradiction to usual physiological findings – the visual threshold was above the pupillomotor threshold. In other words, the pupils sometimes reacted to stimuli which the patients had not seen. Further results of the still ongoing analyses will be presented. A subretinal visual prosthesis was able to elicit pupillary light reflexes.

Conclusions: Pupillary light reflexes and their usual dose-response relationships are preserved in blind RP patients to a larger extend than expected. Investigations in blind RP patients may help to better understand the role of melanopsin ganglion cells in man.

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Pupillary Correlates of Melanopsin Photoreception in Humans

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Objective: A new photoreception process based on light-sensitive pigment melanopsin has been associated with giant retinal ganglion cells that also receive inputs from both rod and cone pathways (Dacey et al., 2005). Such ganglion cells apparently contribute to the pupillary light reflex in humans as well as primates as evidenced by persistence in contraction following light offset (Gamlin et al., 2007). The objective of the present study was to provide both an independent test of the hypothesis that melanopsin photoreception contributes to the human pupil and an alternative method of assessing its contribution. We propose to examine the effects of melanopsin on the pupil in response to the light onset.

Methods: Our study performed new analyses on previously published recordings (Kimura & Young, 1995, 1999). Melanopsin contribution was assessed by investigating differences in the pupillary responses evoked by the onset of photopically equated short- and long- wavelength stimuli (6 sec in duration). As the short-wavelength was selected near the peak and the other wavelength selected toward the tail end of the absorption spectrum of melanopsin, the stimuli should produce predictable differences in photon absorption of melanopsin and thus in the pupillary response amplitudes.

Results: Response comparisons revealed late contraction differences that grew to a peak several seconds after the stimulus onset and fell gradually. The late contraction was associated with short wavelengths and appeared mostly at the higher stimulus intensities, properties that are consistent with those of melanopsin photoreception (e.g., Dacey et al., 2005). Similar comparisons performed in a control condition ruled out possible contributions of confounding effects to the present results.

Conclusions: We conclude that rods and cones are not the only photoreception processes mediating the pupillary light-ON responses in humans and infer that melanopsin is another. Melanopsin photoreception can affect the sustained pupil size in daylight illumination. The present results also suggest that, in conjunction with previous studies on the pupillary correlates of visual acuity (Young & Kennish, 1993; Young et al., 1995), the pupillometric method is capable of providing an opportunity to studying the contribution of melanopsin photoreception to the image-forming as well as non-image-forming pathways of the human visual system.

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Clinical implications of new aspects of the pupil light reflex mediated by melanopsin retinal ganglion cells

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Objective: To understand which stimulus conditions and dynamics of the pupil light reflex help to localize the site of damage in the visual pathway to the outer photoreceptor layer using comparing red and blue light stimuli as a function of light intensity.

Background: New information about the physiology of melanopsin expressing retinal ganglion cells mediating the pupil light reflex and their projections to the brain may provide a basis for localizing the site of damage to the retina in patients with photoreceptor degeneration vs. optic nerve disease.

Methods: Subjects with visual field loss localized to either the photoreceptor layer of the retina or optic nerve were evaluated by recording the pupil light reflex to various types of visual stimuli and comparing them to normal eyes.

Results: Pupil waveform shape, duration, and differential response to low vs. high stimulus intensity and red vs. blue color were useful in localizing the site of damage. Normal eyes showed more sustained pupil response to blue light compared to luminance-matched red stimuli at brighter light intensities. Outer retinal disease showed reduced transient pupil responses, but intact sustained pupil contraction to bright blue stimuli. Optic nerve disease reduced both transient and sustained pupil contractions.

Conclusion: Photoreceptor mediated and intrinsic activation of the melanopsin retinal ganglion cell has both a transient and a sustained pupil response to red and blue light which is intensity dependent. Eyes with severe photoreceptor loss can still maintain a pupil contraction to bright blue light which appears to be mediated by the intrinsic light activation of the melanopsin retinal ganglion cells. Knowledge of response properties and projections of these neurons mediating the pupil light reflex should facilitate localization of damage to either outer photoreceptors or optic nerve.