Selective wavelength pupillometry to evaluate outer and inner retinal photoreception

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ABSTRACT

Purpose: Intrinsically photosensitive retinal ganglion cells (ipRGCs) express a unique photopigment called melanopsin. Capable of direct phototransduction, the ipRGCs are also influenced by rods and cones via synaptic inputs. Thus, the photopigment that mediates the pupil light reflex derives from both outer (rods and cones) and inner (melanopsin-mediated) retinal photoreception. This thesis has aimed to develop a pupillometric test that provides quantitative information about the functional status of outer and inner retinal photoreception in healthy eyes and in eyes with retinal degeneration. In addition to regulating the pupil light reflex, the ipRGCs signal light information for the circadian rhythm, thus, these two non-visual physiologic responses to inner retinal photoreception were examined simultaneously.

Methods: Pupil responses to a long and short wavelength light over a range of intensities (under conditions of light, mesopic and dark adaptation) were recorded using a customized infrared computerized pupillometer. Results were compared for two groups: patients with retinitis pigmentosa and controls. The response function threshold intensity and a half-max intensity was determined from the rod-weighted and cone-weighted pupil responses and correlated to extent of visual loss. The pupil response to light offset was assessed as a measure of direct melanopsin activation. Lastly, pupil responses to red and blue light at equal photo flux were recorded hourly during a 24-hour period and correlated to salivary melatonin concentrations in healthy subjects.

Results: In normal eyes, the blue light evoked greater pupil responses compared to equiluminant red light. With increasing intensity, pupil contraction became more sustained which was most apparent with the brightest blue light. In patients with retinitis pigmentosa, the pupil responses mediated predominantly by rod and cone activation were significantly reduced compared to controls, (p<0.001) and the relative decrease in their contribution resulted in a greater influence of melanopsin on the post-stimulus response. Even at end stage retinal degeneration, pupil responses that derived predominantly from residual cone activity were detectable. The threshold intensity of the rod-mediated, but not cone-mediated, pupil response was also significantly reduced (p=0.006) in patients and the half-maximal intensity of rods correlated with severity of visual loss (r^2=0.7 and p=0.02). In healthy controls, the melanopsin-mediated pupil response demonstrated a circadian modulation whereas the cone-mediated pupil response did not.

Conclusion: Early and progressive loss of rod function in mild-moderate stages of retinitis pigmentosa is detectable and quantifiable as a progressive loss of pupillary sensitivity to extremely dim blue lights obtained under conditions of dark adaptation. In advanced stages of retinal degeneration, chromatic pupillometry is more sensitive than standard electroretinography for detecting residual levels of rod and especially cone activity. In addition, selective wavelength pupillometry can assess non-visual light-dependent functions. The timing of the post-stimulus pupil response to blue light is in phase with melatonin secretion, suggesting a circadian regulation of this pupil parameter.

Key words: pupil, pupil light reflex, melanopsin, photoreceptor, intrinsically photosensitive retinal ganglion cell