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Senescence of the human cone photoreceptor pathways

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Abstract: Color mechanisms dominated by the sensitivity of short-, middle- and long-wave cones have been isolated in individuals from infancy to old age. Losses in sensitivity occur in all three cone mechanisms beginning in adolescence and continuing through later life. These changes are due to both optical and neural factors. Quantitative modeling of threshold vs. intensity functions indicates that much of the neural loss occurs at early stages of retinal processing associated with senescent changes in quantal efficiency rather than increases in neural noise (dark light). Intrinsic compensation mechanisms appear to normalize the balance of cone sensitivities across the life span.

OCIS codes: (330.1720) Color Vision; (330.5310) Photoreceptors; (330.5510) Psychophysics; (999.9999) Aging

Introduction

The proportion of the world's population that is elderly is higher now than at any other point in history. Every month, another one million people enter the sixth decade of life. The consequences of these demographic changes for visual health are profound. Age-correlated changes in visual detection, discrimination and perception greatly affect the quality of life for the elderly, but these changes are still not well understood. The purpose of this paper is to review evidence concerning the sites in the cone pathways responsible for age-related changes in sensitivity.

Human photopic vision is normally trichromatic, due to the presence of three classes of cone photoreceptors, characterized by the wavelength of their peak sensitivity. Studies with the preferential-looking technique have demonstrated that infants can discriminate various pairs of spectral bands, implying that they are least dichromatic (1). However, the spectral identity of the photoreceptors mediating discrimination could not be determined from these studies. Action spectra have been obtained in 4-5 week infants by measuring the visually-evoked cortical potential under conditions of chromatic adaptation for short-wave-sensitive (SWS) cones (2) and silent substitution for middle- (MWS) and long- (LWS) wave-sensitive cones (3). These studies reveal that when sensitivity is specified at the retina, infant cone mechanisms have similar relative spectral sensitivity, but reduced absolute sensitivity, to that of adults. Absolute sensitivity increases after infancy (4) and continues through adolescence (5). Beyond the teenage years, several studies have demonstrated S-cone sensitivity decreases with age (5-10), and some (5,8,10), but not all (9), studies have shown similar losses in the sensitivity of MWS- and LWS-cone mechanisms. Thus, what we call *normal* changes continuously with age and what we call *aging* begins at least by adolescence.

Senescent losses in the sensitivity of cone pathways

Several studies have attempted to measure age-related changes in the sensitivity of individual classes of cone receptors and/or cone pathways (5-10). In most of these studies, sensitivity was measured by increasing the intensity of a monochromatic light superimposed on a chromatic adapting field until the test stimulus reached threshold. The purpose of the adapting field was to suppress the sensitivity of two

of the three classes of cones and the rods, leaving the third cone type isolated to mediate sensitivity (11,12). For example, an intense yellow adapting background will suppress MWS and LWS cones, rendering the SWS cones relatively more sensitive. Under these conditions of chromatic adaptation, a SWS-cone pathway can be isolated for wavelengths below about 510 nm, depending on the intensity of the background. At longer wavelengths, sensitivity is mediated by MWS- and or LWS-cone pathways. Although univariant cone mechanisms are not isolated completely with these methods (13,14), it is nevertheless possible to measure cone sensitivity to a good first approximation over parts of the spectrum. The quality of mechanism isolation can be improved by judicious choice of temporal parameters of the test stimuli owing to the normally slower response of SWS-cone mechanisms (15, *cf.* 16).

For mechanism isolation at longer wavelengths, brief test flashes are more likely to be determined by the quantum catch of a single class of cone (17), whereas longer test flash durations are more likely to be detected through a chromatically-opponent pathway (18).

Eisner *et al.* (6) measured the sensitivity of a SWS-cone mechanism in individuals above 60 years of age and found a significant decline with increasing age. Johnson *et al.* (7) and Werner and Steele (8) sampled evenly over the age range of about 12 to 88 years and found continuous changes in cone sensitivities from about 12 years of age throughout the remaining life span. Figure 1 summarizes the sensitivities of isolated cone mechanisms reported by Werner and Steele (8). Each datum represents average sensitivity across wavelengths in which one cone class dominated sensitivity; SWS cones (440, 460, 500 nm); MWS and LWS cones (500, 530, 560, 590 and 620 nm). The decline in sensitivity with advancing age is significant for each of the three cone classes. Indeed, the slopes of the regression lines shown in the figure were similar for all three cone types and imply a decline of 0.13 ± 0.01 log unit, per decade. Results consistent with these have recently been reported by Knoblauch *et al.* (5) based on a different task, detection of chromatic stimuli falling on dichromatic confusion lines that were embedded in a spatio-temporal achromatic noise field.

Fig.1. Log relative sensitivity (quanta delivered to the cornea) is plotted as a function of age for mechanisms dominated by either SWS- (unfilled squares), MWS- (filled circles), or LWS- (unfilled circles) cone mechanisms. The data are normalized arbitrarily along the sensitivity axis for each cone mechanism. Least-squares linear regression lines are shown for each cone type. Each datum represents one subject's average across a number of wavelengths dominated by the sensitivity of one cone type; see text for details. [Data from Werner and Steele (8).]

Sites of senescent cone sensitivity loss

In all phases of the life span, neural changes in relative and absolute sensitivities of the underlying receptors are difficult to quantify because of correlated developmental changes in ocular media density (19-21) and individual variation in macular pigment (22,23) density. In addition, stimuli

presented in Newtonian view require a correction for age-related changes in pupillary area. Only a few studies have obtained individual measures to correct sensitivities of cone mechanisms for ocular media and macular pigment density, although many have included *estimates* of preretinal factors.

The results presented in Figure 1 refer to sensitivity specified at the cornea and so some of the loss must be attributable to an age-related reduction in retinal illuminance. When these data were corrected for estimated ocular media density changes, SWS-cone sensitivity *at the retina* declines by about 0.08 log unit per decade. This is in agreement with the results of Johnson *et al.* (7) using a similar approach and a more recent study by Werner *et al.* (10) in which ocular media and macular pigment density were measured in separately for each subject. Thus, in these investigations about 40% or more of the age-correlated loss in sensitivity of the SWS cones (defined in terms of light delivered to the cornea at 440 nm) is attributable to light-losses in the ocular media, with the remaining loss ascribable to receptor and/or postreceptor changes. To the extent that the changes in sensitivity for all three cone pathways are similar, relatively greater neural changes would be implied for MWS and LWS mechanisms, but this may perhaps reflect some gain changes supporting constancy of relative cone sensitivity as discussed below.

Histological data have so far provided only a few constraints on hypotheses about the neural loci that may be responsible for functional changes in human cone mechanisms inasmuch as age-correlated anatomical changes are nearly ubiquitous in human visual pathways (but see ref. 24). Candidate sites for age-correlated losses in sensitivity at a neural level include changes in the morphology of cone outer segments (25), density of cones outside the central retina (26,27), displaced nuclei in the outer plexiform layer (29), ganglion cell density (29), and cell loss in the visual cortex (30).

Psychophysical studies have provided more specific information about the sites of senescent losses of sensitivity of cone pathways based upon quantitative modeling of threshold vs. intensity (tvi) functions. Scheffrin *et al.* have shown that age-related changes in detection (31) and discrimination (32) thresholds mediated by an S-cone pathway were dependent on the level of light adaptation. Similar, but less extensive, results were reported for an LWS/MWS-cone pathway. Figure 2 shows mean tvi

Fig. 2. Mean increment threshold functions for younger (open symbols) and older observers (filled symbols) under conditions in which test flash detection was mediated by an SWS-cone pathway. The solid curves show theoretical functions using Eq. [1]. In terms of the model, the difference between younger and older observers is primarily due an age-related reduction in quantal efficiency or an elevation of neural noise. [Data from Scheffrin *et al.* (31).]

functions for groups of younger and older observers under conditions that isolated an SWS-cone mechanism. The task was to detect the presence of a 1_i, 440 nm, test spot superimposed on 470 nm adapting fields and a 570 nm auxiliary field. The two groups of observers differed primarily at low intensities (the plateau or absolute threshold of the mechanism) and then converged at higher intensity.

The data in Figure 2 were analyzed in terms of a modified version of a model of the „₁ pathway (14), according to which SWS-cone signals pass through two serial gain sites. Attenuation at the first site is related to quantal efficiency and spontaneous neural noise. In this context, intrinsic noise is additive noise, also known as *Eigengrau* or dark light (33). Dark light is defined operationally as the intensity of the background where the plateau and rising portions of the tvi function intersect. Attenuation of the test signal at the second site in the model is monotonically related to the *net imbalance* between antagonistic inputs from SWS cones

versus some combination of MWS and LWS cones. Following Pugh *et al.* (34), predicted tvi functions were fitted with the following equation:

$$\begin{aligned} \text{Log}U_{440} = & \log U_{0440} - \log \zeta_1 [k_0 \text{SWS}(A \oplus A)] - \log \zeta_2 [k_1 \text{SWS}(A \oplus A)] \\ & - [k_2 \text{MWS}(A \oplus A)] - k_3 [\text{LWS}(A \oplus A)] \end{aligned} \quad [1]$$

where U_{440} is the threshold at 440 nm in the presence of the 470 nm adapting field of radiance A and the 570 nm auxiliary field of radiance A . $(A \oplus A)$ represents the superposition of the adapting and auxiliary fields. $\text{Log } U_{0440}$ is the absolute threshold of the SWS-cone mechanism for the 440 nm test light. The variables SWS, MWS and LWS represent the normalized rates of quantal absorption by the cones, adjusted for individual subjects based upon estimates of their ocular media density. The gain functions at the level of the SWS cones and the second (postreceptoral) stage are represented by ζ_1 and ζ_2 , respectively, and have the form of Stiles' (36) tabulated increment threshold function, $\zeta(x)$. Parameters k_0 , and k_2 were allowed to vary freely for curve fitting. Following Pugh and Mollon (14), parameters k_1 , k_2 , and k_3 were constrained to satisfy the following equation:

$$0 = k_1 \text{SWS} - k_2 \text{MWS} - k_3 \text{LWS} \quad [2]$$

where $\mu = 500$ nm and $k_2 = k_3$. Reliable differences between younger and older observers were found for parameters $\log U_{0440}$ and k_0 , but not for the other curve-fitting parameters of Eq. [1]. This analysis indicated that, on average, 68% of the sensitivity loss in elderly subjects is due to age-related changes in effective photon capture (quantal efficiency), or an elevation in neural noise. Accounting for the remaining differences in age-related sensitivity losses requires that other neural factors be considered.

While the data and modeling imply that a large proportion of the age-related loss in cone sensitivity is ascribable to changes in early stages of processing, the model cannot distinguish between the effects of quantal efficiency and dark light. The reason is that the rising portions of the tvi functions followed Weber's law, implying a unit slope, or $n = 1.0$ in Eq. [3]:

$$\text{Increment Threshold} = [A (px + D)^n] / p \quad [3]$$

where A is the Weber fraction, x is the field intensity, D is the dark light and p is the proportion of unbleached photopigment (36). Under conditions that follow Weber's law, ($n = 1.0$), either reductions in photopigment (or mathematically equivalent degradations of quantal efficiency) or increases in dark light affect the shape of the tvi curve in the same manner. Because Weber's law was followed in previous aging studies such as illustrated by Figure 2, these two factors could not be separated from one another; both essentially move the curves along a 45° line in log-log coordinates. However, under conditions that are limited by statistical fluctuations in the number of quanta absorbed, following the deVries-Rose law (37,38) with $n = 0.5$, decreases in quantal efficiency and increases in dark light do not produce equivalent shifts in the tvi function. This is illustrated by Figure 3A. Note that photopigment depletion shifts the tvi function such that there is no convergence of the rising portions of the curves. Thus, if tvi functions are measured under conditions in which $n \ll 1.0$, it may be possible to distinguish between the contributions of dark light and quantal efficiency to age-related elevations in photopic thresholds. Barlow (39) has shown that conditions likely to generate a tvi function conforming to the deVries-Rose law are obtained with test stimuli of small area and short duration detected on backgrounds of moderately low intensity.

Tvi functions were measured for 48 subjects, 20 to 88 years of age, using experimental conditions chosen so that thresholds were close to those limited by statistical fluctuations in quantum absorption (deVries-Rose law), thereby permitting the influences of dark light and quantal efficiency to senescent elevations in photopic thresholds to be separated (40). Fig. 3B presents results from one older subject. Each subject's data were fitted simultaneously by four straight lines using a Marquardt least-squares algorithm. Two lines were constrained to a slope of zero, and two lines were unconstrained in their slope. Goodness of fit was evaluated by R^2 (mean = 0.98). Additional tests showed that the

Fig. 3. The left panel shows modeled tvi functions using Eq. [3]. The lowest curve shows a hypothetical young observer, while the upper curves show the predicted shifts for older observers assuming either a 1.0 log unit increase in dark light (>D) or a 1.0 log unit reduction in photopigment quantal catch (<p) compared to the young observer. The middle panel presents the tvi function of an older observer obtained with 560 nm (10 msec, 14.4° diam) test stimuli imaged at 8° in the nasal retina, and superimposed on 500 nm (12.9°) backgrounds. Horizontal and vertical arrows show fitted values corresponding to absolute photopic threshold and photopic dark light, respectively. The right panel shows modeled tvi functions and mean parameters from measured tvi functions obtained from the seven youngest and seven oldest observers in the sample. [Data from Werner *et al.* (40).]

plateaus of the lower and upper tvi functions, defined by the horizontal lines fit to the data, represent absolute thresholds of scotopic and photopic mechanisms, respectively.

As expected from previous work, there was a statistically significant increase in photopic thresholds with increasing age. Photopic dark light values (see vertical arrow, Fig. 3B) were not significantly correlated with age. It is generally accepted that absolute threshold depends upon intrinsic visual noise and quantal efficiency (33). The results of this study showed that while there was a positive correlation between age and photopic threshold, there was no significant correlation between age and dark light. Thus, the results of this study indicate that age-related changes in photopic thresholds are not ascribable to an increase in one type of additive noise, dark light, but are attributable, at least in part, to reductions in quantal efficiency.

The changes in quantal efficiency needed to explain age-related increases in threshold may involve several different factors influencing the ability of the photoreceptors to capture quanta. Candidate mechanisms include morphological changes in the cone outer segments (25), diminished ability to regenerate pigment (41-43), or perhaps some loss of cones outside the central retina (26-28). Two approaches have been used in previous studies to estimate combined losses in MWS- and LWS-cone photopigment density in relation to age, retinal densitometry and psychophysics. Results obtained from densitometry suggest that there are declines in photopigment density of ~0.03 per decade with age (43-46) and that these changes occur primarily in the fovea and less so in the parafovea. There are at least three plausible interpretations for these age-related changes in photopigment OD. They could be due to: (i) a reduction in the length of the cone outer segments, (ii) a change in the alignment of photopigment chromophores that reduces their ability to absorb light, and/or (iii) a reduction in photoreceptor numbers. Psychophysical procedures involving Rayleigh matching have been used to study changes in photopigment density of combined MWS and LWS cones across adulthood. Color matches are not affected by the number of receptors, only by the optical density of pigment within individual receptors. The results obtained from these procedures are inconsistent with one another. Using the color-match effect that measures Rayleigh matches at various retinal illuminances, Elsner *et al.* (47), reported no significant age-related change in the density of MWS-/LWS-cone photopigments.

However, studies measuring differences in the Rayleigh equation for fields of various sizes, the color-match area effect, reveal a calculated decrease in photopigment optical density between 0.01 and 0.02 log unit per decade with a more pronounced effect in the fovea and less so in the parafovea (48). Reductions in photopigment optical density are thus likely to explain a portion of the senescent changes in cone sensitivity, but they are insufficient to explain completely the elevations in the plateau of the tvf function as shown in Figure 3C. Additional factors producing mathematically equivalent photodegradations must be considered to explain these results. Finally, in addition to factors influencing quantal efficiency, age-related degradations not tested in this study may exist such as additive and multiplicative internal noise (49), central inefficiency (50), or intrinsic uncertainty (51). However, other studies have examined senescence of internal noise and have generally not found significant changes (52,53).

Environmental Factors: The Role of Ocular Media and Macular Pigment

The current literature suggests that important sites of age-related losses in the sensitivity of cone pathways are early in retinal processing, most likely within the photoreceptors themselves. It is unclear from these studies, however, why such changes occur in the first place. One view is that light itself may contribute to changes in cone pathways (54). High energy photons from the UV and short-wave visible regions of the spectrum can initiate destructive chain reactions through lipid peroxidation and the formation of singlet-state oxygen and oxygen free radicals. The photoreceptors, which have a high polyunsaturated fat content, may be particularly vulnerable because visual transduction occurs in an environment that requires high oxygen levels. A number of antioxidant defenses are present in the retina (*e.g.*, α -tocopherol, glutathione, melanin, selenium and ascorbic acid), which help to protect from lipid peroxidation. The relevance of studies on light damage by brief, intense exposures to age-related changes under chronic, less intense, exposures is based partly on evidence that retinal damage by photochemical processes is additive over time and intensity (55). This additivity is not complete, though, because rods and cones are capable of molecular renewal (56). Rods can replace the entire length of their outer segments in about two weeks. Renewal of cone outer segments involves piecemeal replacement of molecular constituents and is considerably slower than molecular renewal in rods. Cones may, therefore, be less resilient in their recovery following actinic insult.

That light might contribute to foveal sensitivity losses was demonstrated (57) with eight patients who had undergone bilateral cataract surgery and implantation of intra-ocular lenses (IOLs). The same surgeon and technique were used for both eyes, but one IOL contained UV-absorbing chromophores and the other did not. Hence, the latter lens did not prevent UV radiation (between 320 and 400 nm) from reaching the retina. After five years of differential light exposure of the two retinae, the foveal SWS cones of the eye receiving more UV exposure were about 1.7 times less sensitive than the SWS cones of the other eye. These results are consistent with the hypothesis that light itself may contribute to senescence of the photoreceptors.

Much of the UV radiation incident on the normal eye is absorbed before it can reach the retina; the amount depends on the age of the observer (21). This may provide a natural defense against the most hazardous radiation in natural light sources. In addition, the macular pigment, a yellow photostable pigment that lies in the receptor fiber layer and inner plexiform layer (58), may act as an additional defense by absorbing some of the high-energy photons contained in short wavelengths from the visible spectrum. The macular pigment might also provide an active photochemical defense for the fovea as it is comprised of carotenoid pigments that tend to neutralize photosensitized molecules (59) and inhibit free radical reactions (60). The relations between normal aging, age-related disease, and light-induced retinal damage are complex, but there are some remarkable parallels among them (61-64).

Haegerstrom-Portnoy (65) suggested that the macular pigment may protect the fovea from some hazardous effects of light. She reported that sensitivity losses in a SWS-cone mechanism of an older

group of observers, relative to young controls, were less in the fovea where the density of the macular pigment is highest, than in the parafovea. Consistent with this study, Hammond *et al.* (66) showed that older individuals with high macular pigment density had higher SWS-cone sensitivity (specified at the retina) than individuals of the same age having lower macular pigment density. However, the former study did not include direct measures of macular pigment density and the latter study did not compare cone sensitivities in the fovea and a parafoveal location with little macular pigment. These methodological considerations are important in view of an alternative hypothesis. It might be that long-term adaptation or gain changes in the foveal SWS cones results in higher sensitivity that is directly related to the reduction in short-wave light due to macular pigment screening. The macular pigment protection hypothesis and the compensation hypothesis both predict a positive correlation between macular pigment density and foveal SWS-cone sensitivity compared to parafoveal SWS-cone sensitivity (specified at the retina), but only the former predicts that this correlation should be age dependent.

To evaluate these hypotheses about the role of macular pigment in long-term regulation of the sensitivity of cone pathways, sensitivity of SWS-, MWS- and LWS-cone mechanisms was measured at three retinal loci (fovea, 4_i and 8_i temporal retina) that differ in their pre-receptor screening by macular pigment. In view of the dependence of age-related losses in sensitivity on the level of light adaptation (31; Figure 2), foveal and parafoveal increment thresholds were measured on the plateau of the threshold vs. intensity function of each isolated mechanism, and were referred to the retina using individual measurements of ocular media and macular pigment density. Linear age-related increases in foveal thresholds, specified at the retina, were found for all three cone mechanisms. Parallel sensitivity losses for each cone mechanism were also obtained at 4_i and 8_i in the temporal retina. No significant relation was found between macular pigment density and the age-related change in absolute thresholds obtained from these healthy observers under conditions of foveal S-cone isolation. As illustrated by Figure 4, a significant positive correlation was found between foveal macular pigment density and the SWS cone, but not MWS and LWS cone, sensitivity difference (0_i-8_i) specified at the retina. This

Fig. 4. Log sensitivity difference (0_i-8_i) for a SWS-cone mechanism is plotted as a function of peak macular pigment density. [Data from Werner *et al.* (10).]

relation is consistent with previous evidence that the macular pigment protects the photoreceptors from senescent changes (65,66). In this study, however, the relation between macular pigment and the 0_i-8_i difference in SWS-cone sensitivity was not age dependent, and can be interpreted as due to local gain changes resulting from differential macular pigment screening between the fovea and parafovea. Thus, while there is evidence that the macular pigment may afford some protection for SWS cones during senescence, evaluation of this effect is complicated by gain changes that may compensate for lower stimulation in order to maintain a balance of cone sensitivities across the retina, and across the life span.

Conclusions and Implications for Color Appearance

Significant age-related losses in cone pathways begin around the time of adolescence and continue over the remaining life span. These sensitivity losses have been demonstrated for all three cone

mechanisms and in parafoveal as well as foveal locations. The ocular media and macular pigment selectively screen UV- and short-wave-visible radiation, respectively, and, therefore, alter the spectral sensitivity of cone mechanisms specified at the cornea. Although the shapes of the spectral sensitivity functions cannot be compensated by univariant cone mechanisms, their overall sensitivities can be rescaled by mechanisms of adaptation. Evidence for this kind of adaptation is provided by the relation between macular pigment density and the threshold difference between two retinal areas differing in macular pigment screening.

Mechanisms that compensate for age-related changes in ocular media density or variations in the spatial distribution of macular pigment would promote constancy of color appearance across the life span. A number of studies, using different methods or probing different regions of color space, have demonstrated a substantial degree of stability in color appearance across the life span. (67-69) Analyses of these data indicates that such stability would be possible only if the visual system actively recalibrates itself (68,70). Renormalization of sensitivities of cone pathways would be consistent with the data presented here and would also support perceptual stability across the life span.

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