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Speed, sensitivity, and stability of the light response in rod and cone photoreceptors: Facts and models

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ABSTRACT

The light responses of rod and cone photoreceptors in the vertebrate retina are quantitatively different, yet extremely stable and reproducible because of the extraordinary regulation of the cascade of enzymatic reactions that link photon absorption and visual pigment excitation to the gating of cGMP-gated ion channels in the outer segment plasma membrane. While the molecular scheme of the phototransduction pathway is essentially the same in rods and cones, the enzymes and protein regulators that constitute the pathway are distinct. These enzymes and regulators can differ in the quantitative features of their functions or in concentration if their functions are similar or both can be true. The molecular identity and distinct function of the molecules of the transduction cascade in rods and cones are summarized. The functional significance of these molecular differences is examined with a mathematical model of the signal-transducing enzymatic cascade. Constrained by available electrophysiological, biochemical and biophysical data, the model simulates photocurrents that match well the electrical photoresponses measured in both rods and cones. Using simulation computed with the mathematical model, the time course of light-dependent changes in enzymatic activities and second messenger concentrations in non-mammalian rods and cones are compared side by side.

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1. Introduction

In the dark, rod and cone photoreceptors of the vertebrate retina sustain a circulating ionic current that flows along the extracellular space from the inner to the outer segment (Hagins et al., 1970). The circulating current is an outward K^+ ion flux across the inner segment membrane mediated by voltage-gated K^+ channels (Bader et al., 1982; Hestrin, 1987; Barnes and Hille, 1989; Maricq and Korenbrot, 1990a, b) and an inward Na^+ and Ca^{2+} ion flux across the outer segment membrane mediated by cyclic nucleotide-gated ion channels (CNG channels) (Fesenko et al., 1985; Yau and Nakatani, 1985a). Light suppresses this current by closing the outer segment CNG channels and, as a consequence, the cell membrane potential hyperpolarizes (Baylor and Fuortes, 1970; Tomita, 1971; Baylor and Hodgkin, 1973; Schwartz, 1973) initiating the process of vision.

The functional features of the light response of rods and cones are well suited to the ecological needs of vertebrate behavior. Thoroughly dark adapted rods yield a detectable signal, a signal larger than their intrinsic noise, when only a single visual pigment molecule is excited by light (Baylor et al., 1979b) while cones yield a detectable signal only when light flashes excite 4–10 visual pigment (VP) molecules per cell (Naarendorp et al., 2010; Koenig and Hofer, 2011; Korenbrot, 2012). Cones adjust their photosensitivity as a function of mean background intensity, and thus can respond to changes over 9 log units of light intensity (Burkhardt, 1994), the range of illuminance from a clear night sky (2×10^{-3} lux) to that by direct sunlight (1.3×10^{5} lux) (Wikipedia.org). Rods, however, adapt over a smaller range of light intensities than do cones (Baylor et al., 1984; Fain et al., 1989; Matthews et al., 1990; Schnapf et al., 1990). Indeed, under bright steady illumination the outer segment dark current can be fully suppressed in rods (response saturation), but not in cones (response cannot be saturated) (Jones et al., 1993; Burkhardt, 1994; Kenkre et al., 2005). In cones, extremely intense steady light suppresses the circulating current for only a brief moment and it then recovers to a new steady value, reflecting reopening of the CNG channels. In human cones, for example, when over 90% of the visual pigment (VP) is bleached, the dark current amplitude is only half that measured in the dark (Kenkre et al., 2005) and the same is observed in cones of non-mammalian species (Jones et al., 1993).

Over the first six log units of light intensity above threshold, cones respond with constant contrast. That is, flashes of a given intensity measured as a percentage of the background intensity generate the same amplitude response regardless of the absolute magnitude of the background light (Normann and Werblin, 1974; Normann and Perlman, 1979; Burkhardt and Gottesman, 1987; Burkhardt, 1994). This feature allows cones to respond over about two log units of light intensity centered on the background level, regardless of the absolute background intensity (Burkhardt and Gottesman, 1987; Perlman and Normann, 1998). This is also the range of intensities relative to the mean background level typical of natural scenes (Mante et al., 2005). The time course of the light response is faster in cones than in rods, and can inform of changes in illuminance as frequent as every 100–200 ms, for example, the interval between eye saccades typical in language reading (Blythe et al., 2006). The chromatic range of the cone response, summed over the absorbance spectra of all known cone opsins (with peak absorbance ranging from 360 nm to 630 nm) is well tuned to the solar spectral irradiance on earth's surface, a spectrum that ranges from 220 nm to 2400 nm with a single peak at 500 nm (Thuilier et al., 2003).

Rod and cone photoresponses differ in any given vertebrate species, yet both are extremely stable and reproducible. This reflects the exceptional regulation of the cascade of enzymatic reactions that link VP excitation by light to the gating of the CNG ion channels. This enzymatic transduction pathway accomplishes the same task in both receptor types but with different speed, photosensitivity and light and dark adaptation features. The extensive biochemical and biophysical information on the transduction pathways in rods and cones can be difficult to reduce into a single coherent view. Mathematical models offer a succinct and precise tool to describe and understand physiological processes based on the function of the molecules that constitute the processes. Starting with the pioneering mathematical models of phototransduction by Tranchina and Sneyd in cones (Sneyd and Tranchina, 1989; Tranchina et al., 1991) and Forti et al. in rods (Forti et al., 1989; Torre et al., 1990), ever improving, coherent models of phototransduction have evolved to include new and refined biochemical and biophysical information. A number of contemporary models have been developed that quantitatively describe the full complement of reactions involved in the phototransduction pathway. Among them are: rods (Pugh and Lamb, 1993; Hamer et al., 2003, 2005; Caruso et al., 2010; Shen et al., 2010); cones (Reingruber and Holcman, 2008; Soo et al., 2008; Korenbrot, 2012). These models share many specific features and generally address either rod or cone phototransduction. In this review, we explore quantitative differences and similarities between the biochemical and biophysical reactions of the phototransduction pathways in rods and cones. We compare and contrast the differences and similarities using the same, comprehensive mathematical model of phototransduction (Korenbrot, 2012). This model evolves from, and incorporates many features common to preceding models and adds recently discovered regulatory events, particularly with respect to feedback control by cytoplasmic Ca^{2+}. The efficacy of the model and the functional significance of many of the molecular differences between the rods and cones are verified by matching simulated and experimental photocurrents measured in dark-adapted photoreceptors.

2. Brief overview of the evolution of the signal transduction pathway of vertebrate photoreceptors

Evolution of the eye can now be traced from ancient multicellular organisms, related to corals and jellyfish, to humans (Schwab,