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Origin and Functional Impact of Dark Noise in Retinal Cones

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Summary

Spontaneous fluctuations in the electrical signals of the retina's photoreceptors impose a fundamental limit on visual sensitivity. While noise in the rods has been studied extensively, relatively little is known about the noise of cones. We show that the origin of the dark noise in salamander cones varies with cone type. Most of the noise in long wavelength–sensitive (L) cones arose from spontaneous activation of the photopigment, which is a million-fold less stable than the rod photopigment rhodopsin. Most of the noise in short wavelength–sensitive (S) cones arose in a later stage of the transduction cascade, as the photopigment was relatively stable. Spontaneous pigment activation effectively light adapted L cones in darkness, causing them to have a smaller and briefer dim flash response than S cones.

Introduction

Studies of the dark noise in the membrane currents of rod photoreceptors have provided insights into the operation of the phototransduction cascade (Baylor et al., 1980; Rieke and Baylor, 1996) as well as the processing of rod light responses in the retina (Bialek and Owen, 1990). Two components dominate the rod's dark noise: discrete photon-like events caused by spontaneous activation of rhodopsin, and continuous current fluctuations caused by spontaneous activation of phosphodiesterase (Baylor et al., 1980; Rieke and Baylor, 1996). Measurements of the rod's dark noise are in good agreement with the noise that limits behavioral sensitivity (Baylor et al., 1984; Aho et al., 1988; Rieke and Baylor, 1998), indicating that noise in the rods rather than in central neurons limits the absolute sensitivity of rod vision. Retinal cones have more dark noise than rods (Lamb and Simon, 1977; Schnapf et al., 1990; Schneeweis and Schnapf, 1999), and behavioral thresholds of cone vision are higher (Barlow, 1957). However, neither the molecular origin of the cone noise nor its functional implications are known.

Barlow suggested that the higher dark noise of cone vision could be accounted for by an increased rate of thermal activation of the L cone photopigment (Barlow, 1957). According to this hypothesis, thermal fluctuations would cause the rate of spontaneous activation to be higher for photopigments absorbing at long wavelengths (e.g., the L cone pigment) than those absorbing at short wavelengths (e.g., the rod or S cone pigments). Although this idea may help account for the difference in behavioral sensitivity of rod and cone vision, it has not been tested experimentally.

Previous measurements suggest that the dark noise of cones, like that of rods, is dominated by two components. In primate cones, bleaching the photopigment reduced the dark noise in the membrane current, suggesting that at least some of the noise originated from spontaneous pigment activation (Schnapf et al., 1990). However, in primate (Schneeweis and Schnapf, 1999) and turtle (Lamb and Simon, 1977) cones the frequency composition of the dark voltage noise often differed from that of the dim flash response, suggesting an additional noise source downstream of the photopigment either in the transduction cascade or in the inner segment. We examined the relative magnitudes of these two components of dark noise in salamander L and S cones and investigated the impact of the noise on cone signaling.

Results

We used suction electrodes (Baylor et al., 1980; Rieke and Baylor, 1996) to study the fluctuations in the outer segment membrane currents of salamander L and S cones, identified by the relative amplitudes of their responses to 380, 440, and 620 nm light (see Experimental Procedures). The measured current fluctuations consisted of instrumental noise as well as cellular noise. The instrumental noise was isolated by exposing the cell to a bright saturating light that eliminated the membrane current by closing all the channels in the outer segment (Figures 1A and 1B). The additional noise present in darkness was produced by cellular fluctuations; as described below, the properties of this cellular noise differed for L and S cones.

The first indication that the noise in the L and S cones had different origins came from measuring the component of cellular dark noise requiring the presence of the dark-adapted photopigment. Current fluctuations were measured before and after bleaching $>$99% of the photopigment and allowing the dark current to recover. Figure 1 shows sections of record in darkness, saturating light, and after bleach from an L cone (Figure 1A) and an S cone (Figure 1B). Figures 1C and 1D show power spectra of the current fluctuations measured in each condition. Bleaching the photopigment substantially reduced the dark noise in L cones (Figure 1C). Bleaching the S cone photopigment, however, increased slightly or did not change the dark noise (Figure 1D); the increase in noise seen after bleach in some S cones may be due to residual activity of the bleached photopigment as occurs in rod photoreceptors (Leibrock et al., 1994). In six L cones, the current variance between 0.2 and 10 Hz was 0.18 $\pm$ 0.07 pA^2 in darkness, while the variance after bleaching the photopigment was 0.010 $\pm$ 0.003 pA^2 (mean $\pm$ SEM); in 4 S cones the variance in darkness

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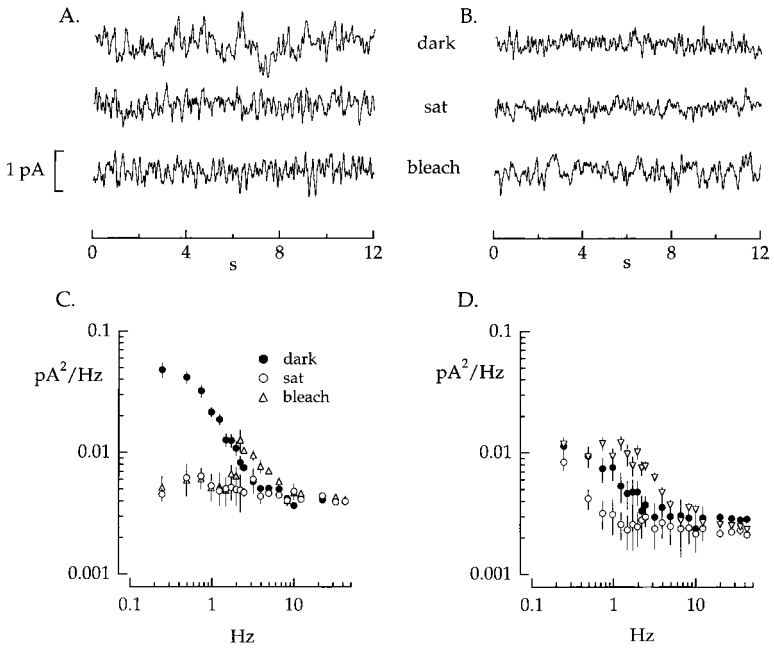

Figure 1. Properties of the Dark Noise in L and S Cones

(A) Membrane current from an L cone recorded in darkness, in the presence of a saturating light, and after bleaching >99% of the photopigment and allowing the dark current to recover. The light intensity used to saturate the cone was just sufficient to eliminate the dark current and thus isolate instrumental noise. This condition could be maintained for 1–2 minutes by gradually increasing the light intensity to compensate for the decrease in sensitivity caused by photopigment bleaching. After the saturating light was applied, the cell's remaining photopigment was bleached by an intense light (>10^8 photons μm^{-2} s^{-1}) presented for 5–10 min. Recording bandwidth, 0–10 Hz.

(B) Membrane current from an S cone for the same conditions as in (A).

(C) Power spectra of current fluctuations from the L cone of (A). In each condition 15–35 epochs of current were recorded and each epoch was used to estimate the power spectrum. The points show the mean and SEM in darkness (closed circles), in saturating light (open circles), and after bleach (open triangles). Recording bandwidth, 0–200 Hz; currents digitized at 1 kHz.

(D) Power spectra of current fluctuations from the S cone of (B), computed as in (C).

was 0.05 ± 0.02 pA^2 and after bleaching was 0.08 ± 0.03 pA^2 (mean ± SEM). Thus, most of the dark noise in the L cones required the presence of the dark-adapted photopigment, while the noise in the S cones did not. This result suggests that spontaneous photopigment activation dominates the L cone but not S cone dark noise.

The power spectrum of the dark noise in L and S cones provided further evidence for a difference in the rates of spontaneous pigment activation. Assuming the cellular dark noise and instrumental noise are independent and additive, the power spectrum of the cellular noise can be isolated as the difference (dark − sat). Figure 2 compares the power spectra of the cellular dark noise and the dim flash response for the L and S cones from Figure 1; the flash response spectra have been scaled vertically for comparison with the dark noise spectra. In L cones the frequency composition of the dark noise was similar to that of the dim flash response (Figure 2A; similar results in six L cones), consistent with noise produced by a random superposition of elementary events with a time course like that of the single photon response. In S cones the spectrum of the dark noise differed from the spectrum of the dim flash response (Figure 2B; similar results in five S cones), indicating that the elementary events producing the noise had a different time course than the cell's single photon response.

Experiments on truncated cone outer segments (Figure 3A) provided a third piece of evidence for a difference in the rate of spontaneous pigment activation in L and S cones. Spontaneous photopigment activation

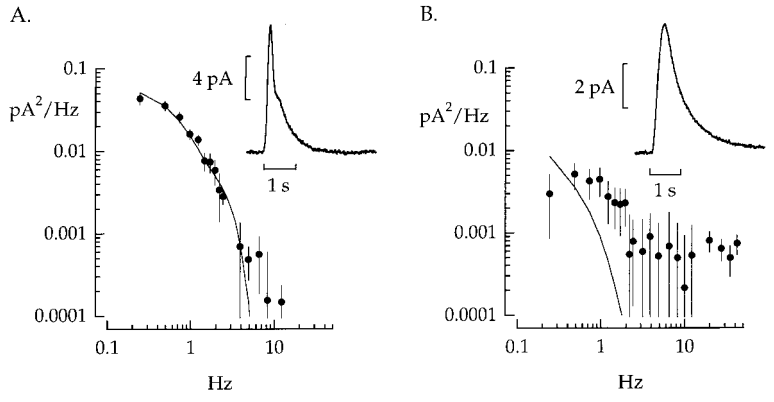

Figure 2. Comparison of Power Spectra of Dark Noise and Dim Flash Response from an L Cone and an S Cone

(A) Cellular dark noise spectrum from the L cone of Figure 1. Assuming the cellular dark noise and instrumental noise are independent and additive, the dark noise can be isolated as the difference spectrum (dark − sat), which is plotted as the closed circles. The smooth curve is the power spectrum of the cell's response to a 10 ms flash delivering 260 photons μm^{-2} at 620 nm; the flash response itself is shown in the inset. The power spectrum of the flash response has been scaled vertically to fit the dark noise spectrum, with a scale factor corresponding to an isomerization rate of 680 photons μm^{-2} s^{-1}.

(B) Difference spectrum (dark − sat) compared with the power spectrum of the flash response from the S cone of Figure 1. The response to a 10 ms flash delivering 61 photons μm^{-2} at 440 nm is shown in the inset. The vertical scale factor for the spectrum of the flash response corresponds to an isomerization rate of 1.5 photons μm^{-2} s^{-1}.

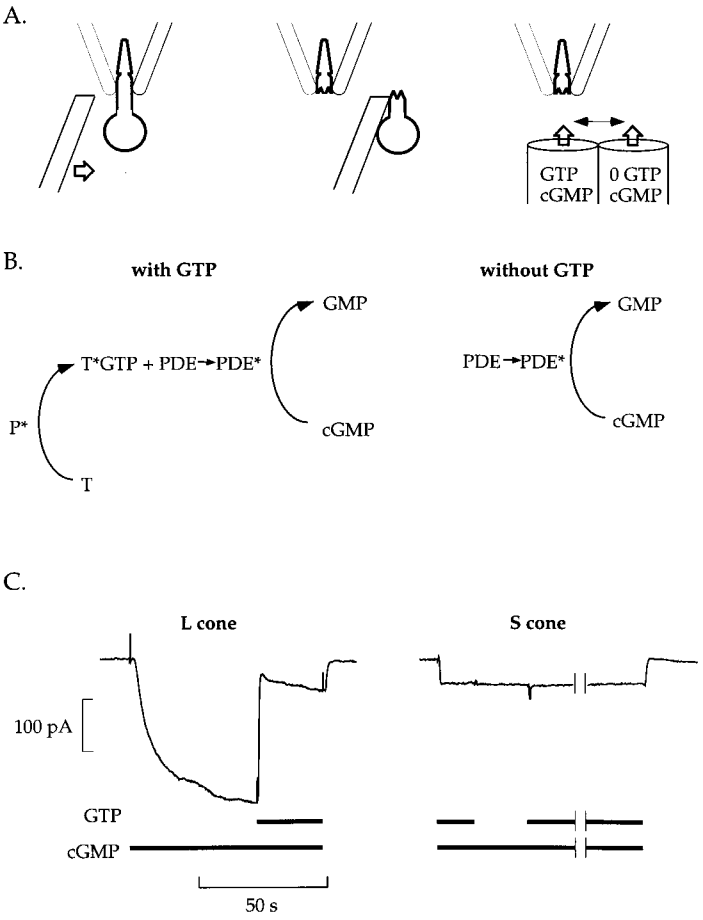

Figure 3. Evidence for GTP-Dependent Spontaneous Phosphodiesterase (PDE) Activity in L Cones but Not S Cones

(A) L and S cones were truncated, providing diffusional access to the inside of the outer segment and permitting the internal solution to be changed by flowing different dialyzing solutions across the cut end of the cell (see Experimental Procedures). To minimize possible contamination from light-activated transducin, no visible light was delivered to the outer segment after truncation.

(B) Removing GTP from the dialyzing solution effectively eliminates the contributions of the photopigment and transducin to the PDE activity in the transduction cascade.

(Left) Activated photopigment molecules (P*) normally cause a decrease in cGMP concentration by catalyzing GDP–GTP exchange on transducin (T), causing it to become active (T*GTP). Active transducin in turn activates phosphodiesterase (PDE), which hydrolyzes cGMP.

(Right) In the absence of GTP, transducin activation is prevented, and any cGMP hydrolysis occurs only as the result of spontaneous PDE activity.

(C) Results from GTP removal experiments on an L cone (left) and an S cone (right). Timing of changes in the dialyzing solution are indicated in the lower traces. Initially, the outer segments were dialyzed with a solution lacking GTP and cGMP. In the L cone, the dialyzing solution was first changed to one containing 75 μM cGMP but no GTP, producing a large current. Changing the dialyzing solution to one containing 10 μM GTP caused a large decrease in current, indicating substantial activation of PDE by transducin in the absence of light. In the S cone, a dialyzing solution containing 10 μM GTP and 75 μM cGMP produced a current indistinguishable from that produced by cGMP alone, indicating little or no transducin-dependent activation of PDE.

should increase the activity of subsequent stages of the transduction cascade. Thus, active photopigment activates the G protein transducin, which then activates phosphodiesterase (PDE), causing the cGMP level to fall and the membrane current to decrease (Figure 3B). If the photopigment is spontaneously active, suppressing transducin activation will decrease the dark PDE activity and cause the membrane current to increase. We tested this prediction by suppressing transducin activation and observing the effect on the membrane current. Truncated L and S cone outer segments were dialyzed with a solution containing no GTP and 75 μM cGMP, a condition that suppressed transducin activation, or a solution containing 10 μM GTP and 75 μM cGMP, a condition that permitted transducin activation but supported little cGMP synthesis, as in truncated rod outer segments (Lagnado and Baylor, 1994). When the outer segment was dialyzed with the solution lacking GTP, the photopigment was unable to activate transducin, and the outer segment ceased to respond to light. In five L cone outer segments, the current in the absence of GTP was between 2.2 and 5 times larger than in the presence of GTP (Figure 3C). In three S cone outer segments, the current in the presence and absence of GTP differed by <10% (Figure 3C). Thus, L cones but not S cones had substantial dark transducin activity.

The reduction in noise after bleaching the photopigment (Figure 1), the similarity of the power spectra of the dark noise and dim flash response (Figure 2), and the high dark transducin activity (Figure 3) indicate that the L cone dark noise is caused by spontaneous activation of the photopigment. In contrast, in S cones the insensitivity of the noise to bleaching of the pigment, the difference between the dark noise and dim flash spectra, and the lack of dark transducin activity indicate a low rate of spontaneous pigment activation. The rate of spontaneous activation of each photopigment was estimated from the scale factor required to fit the dark noise power spectrum with the power spectrum of the dim flash response (e.g., Figure 2A). In six L cones, the estimated rate of spontaneous activation was 600 ± 200 s^{-1} (mean ± SEM). In five S cones, the spontaneous activation rate was <2 s^{-1}, although the absolute rate could not be determined because of the different shapes of the noise and dim flash spectra. For comparison, the photopigment in salamander rods activates spontaneously at a rate of about 0.03 s^{-1} (Vu et al., 1997). As a salamander rod contains about 30 times as many photopigment molecules as a cone, the L cone pigment is about 6×10^5 times less stable than rhodopsin.

The high rate of spontaneous pigment activation effectively light adapted L cones even in darkness, caus-

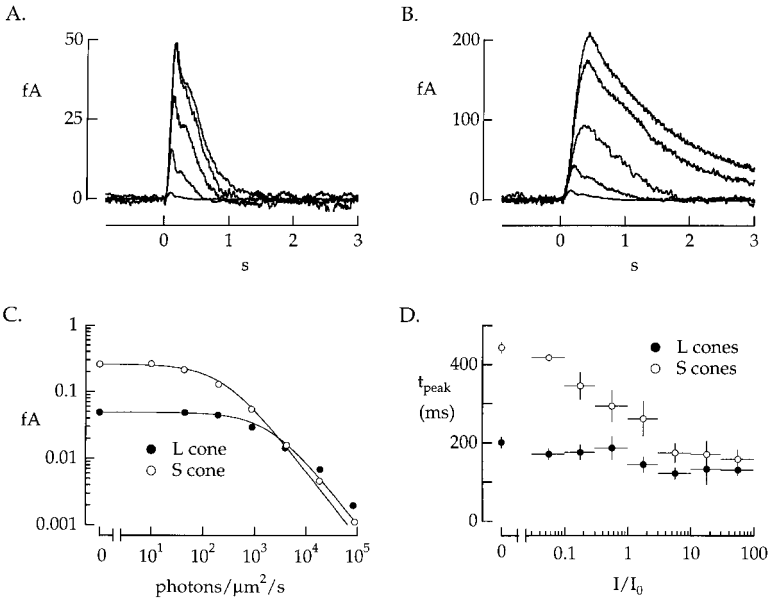

Figure 4. Effect of Steady Illumination on the Single Photon Response of L and S Cones

(A) Estimated single photon responses of an L cone in darkness (largest response) and in the presence of steady light of 198, 912, 3,981, and 83,000 photons μm^{-2} s^{-1} at 620 nm. The dim flash response measured at each steady light level was scaled by the number of photoisomerizations produced by the flash assuming a collecting area of 1 μm^2 (Perry and McNaughton, 1991).

(B) Estimated single photon responses of an S cone in darkness (largest response) and in the presence of steady light of 44, 203, 886, and 4,230 photons at $\mu m^{-2}s^{-1}$ at 440 nm.

(C) Dependence of estimated single photon response amplitude on steady light intensity for the L and S cones from (A) and (B). Smooth curves fitted to the measurements are calculated according to Equation 1 with I_0 = 250 photons $\mu m^{-2}s^{-1}$ for the S cone and 2,100 photons $\mu m^{-2}s^{-1}$ for the L cone.

(D) Collected results on the dependence of the time to peak of the dim flash response on steady light intensity for seven L cones (closed circles) and five S cones (open circles). Steady light intensities have been scaled by the intensity I_0 at which the estimated single photon response was half as large as that in darkness (see [C] and text). As different background intensities were used in each experiment, each point represents the average time to peak for all measurements in the intensity range covered by the horizontal error bars. Vertical error bars represent SEM.

ing them to have a smaller and briefer dim flash response than S cones. For dim flashes producing the same number of photoisomerizations, the response of a dark-adapted S cone was larger and rose for a longer time than that of an L cone (Figure 4). The estimated single photon response amplitude was 0.23 ± 0.03 pA (mean ± SEM) in five S cones versus 0.04 ± 0.01 pA in seven L cones, while the time to peak was 440 ± 60 ms in the S cones versus 200 ± 26 ms in the L cones, differences first observed by Perry and McNaughton (1991). These differences in the L and S cone dim flash responses decreased in the presence of steady light (Figures 4A and 4B), presumably as the photoisomerizations produced by the steady light exceeded the isomerizations due to spontaneous activation. Figure 4C shows the dependence of the response amplitude on steady light intensity for the L and S cones of Figures 4A and 4B. The smooth curve fitted to the data is given by

$$R = \frac{R_D}{1 + I/I_0}, \quad (1)$$

where R is the response amplitude, R_D is the amplitude in darkness, I is the steady light intensity, and I_0 is the intensity required to halve the response. I_0 was 340 ± 130 photons μm^{-2} s^{-1} in five S cones (mean ± SEM) and 1200 ± 400 photons μm^{-2} s^{-1} in seven L cones. Thus, in darkness the single photon response in S cones was more than 5 times larger than that in L cones, but this difference decreased to less than a factor of 2 in bright steady light. Steady lights also decreased the difference in the time to peak of the S and L cone responses, as shown in Figure 4D. In bright light, the time to peak of the responses in the two cone types was not measurably different.

The experiments summarized in Figure 4 allowed us to compare the single photon responses in L and S cones with similar total pigment activation rates (photoisomerizations plus spontaneous isomerizations). Thus, with a collecting area of 1 μm^2 (Perry and McNaughton, 1991), an S cone exposed to a steady light with an intensity of 600 photons μm^{-2} s^{-1} has a pigment activation rate similar to that of an L cone in darkness. At this steady light level, the single photon response of the S cones had an amplitude of 50–100 fA and took 220–280 ms to reach peak. This is similar to the response of a dark-adapted L cone, suggesting that much of the difference in the dark-adapted responses of the two cone types can be attributed to the differences in the rates of spontaneous pigment activation.

Dim steady light also produced substantially more noise in S cones than in L cones, consistent with the larger single photon response and lower dark noise of the S cones. Figure 5 shows sections of record in the presence of steady background light, in darkness and in saturating light for an L cone (Figure 5A) and an S cone (Figure 5B). The light-induced current fluctuations were larger in the S cone than the L cone. As expected for light-induced fluctuations, the power spectrum of the light-dependent noise had the form of the power spectrum of the dim flash response for both L cones (Figure 5C) and S cones (Figure 5D). Figure 5E shows collected results on the dependence of the current variance between 0.2 and 10 Hz on the steady light intensity.

Discussion

The experiments described above indicate that the molecular origin of the dark noise in the membrane current of salamander L and S cones differs. Noise in the L cones is dominated by spontaneous activation of the photopigment, and the contribution from other components of the transduction cascade is relatively small.

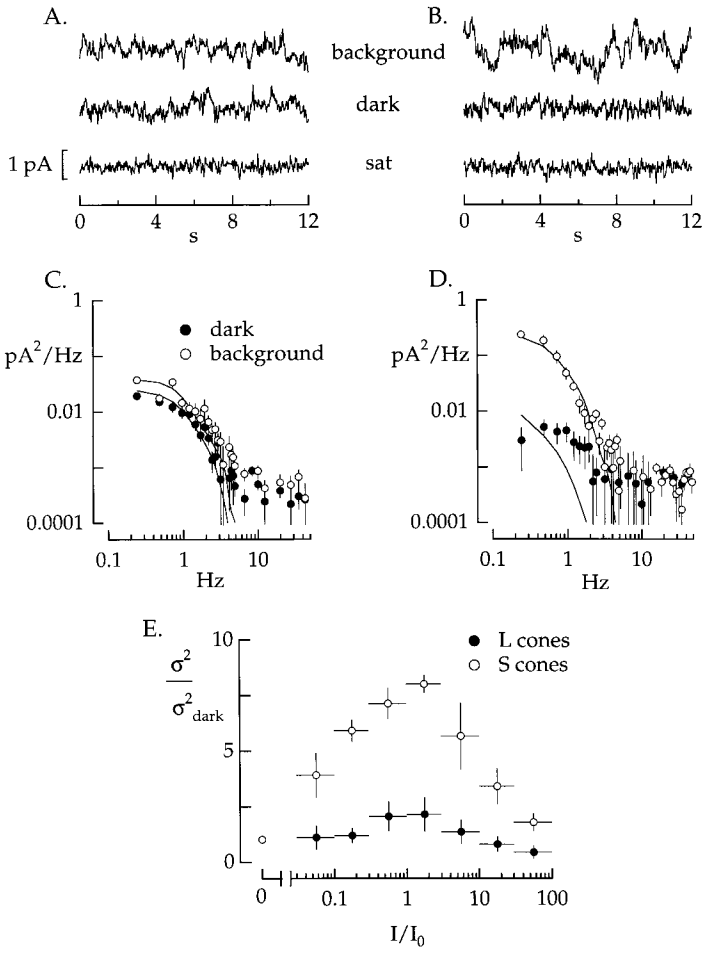

Figure 5. Effect of Steady Illumination on the Current Noise of L and S Cones

(A) Membrane current fluctuations from an L cone in steady light with an intensity of 290 photons $\mu m^{-2}s^{-1}$ at 620 nm, in darkness and in saturating light.

(B) Membrane current fluctuations measured from an S cone in steady light with an intensity of 140 photons $\mu m^{-2}s^{-1}$ at 440 nm, in darkness and in saturating light.

(C) Power spectral densities of the current noise from the L cone of (A) measured in darkness (closed circles) and in the presence of a steady light with an intensity of 290 photons $\mu m^{-2}s^{-1}$ at 620 nm (open circles). The cellular noise has been isolated by subtracting the instrumental noise measured in saturating light (see Figure 1). The smooth curves are the power spectra of the cell's dim flash responses measured in darkness and in steady light, scaled vertically to fit the noise spectra. The vertical scaling factors correspond to isomerization rates of 460 s^{-1} in darkness and 755 s^{-1} in steady light. Bandwidth, 0–200 Hz; currents digitized at 1 kHz.

(D) Current noise measured in the S cone of (B) in darkness and in the presence of a steady light with an intensity of 140 photons $\mu m^{-2}s^{-1}$ at 440 nm. The smooth curves are the power spectra of the corresponding dim flash responses, scaled vertically to fit the noise spectra. The vertical scaling factors correspond to isomerization rates of 1.5 s^{-1} in darkness and 96 s^{-1} in steady light.

(E) Collected measurements of the current variance between 0.2 and 10 Hz as a function of mean light intensity for six L cones (closed circles) and four S cones (open circles). Light intensities have been scaled as in Figure 4D, and for each cell the variance measured at each steady light intensity has been normalized by the dark variance. Error bars as in Figure 4D.

Noise in the S cones arises downstream of the photopigment in the transduction cascade. By analogy with the continuous noise of rod photoreceptors (Baylor et al., 1980; Rieke and Baylor, 1996), a possible source of the S cone noise is spontaneous activation of the phosphodiesterase. Indeed, the phosphodiesterase in S cones differs from that of other cone types (Hamilton and Hurley, 1990).

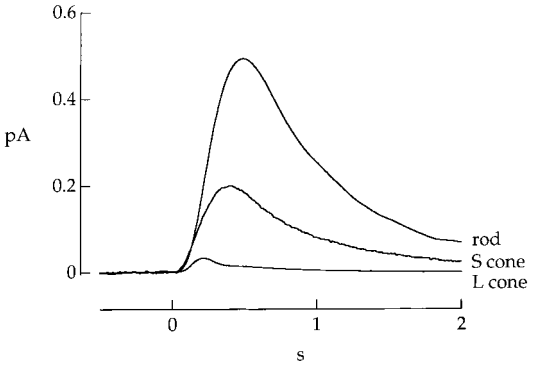

Figure 6. Single Photon Responses in a Rod, an S Cone, and an L Cone

The single photon response was estimated by dividing the average response to a dim flash by the number of photoisomerizations produced by the flash, assuming a collecting area of 1 μm^2 for the L and S cones and 15 μm^2 for the rod. The flash strength was 0.53 photons μm^{-2} for the rod, 24 photons μm^{-2} for the S cone, and 240 photons μm^{-2} for the L cone.

The observation that spontaneous photopigment activation proceeds at a higher rate in L cones than in rods or S cones is in qualitative agreement with Barlow's hypothesis (Barlow, 1957) that the spontaneous activation rate is determined by the energy of the photons to which the pigment is most sensitive. However, the apparent energy barrier for thermal activation of the rod photopigment rhodopsin is only about half the energy of a photon at the wavelength of rhodopsin's peak sensitivity (Baylor et al., 1980). This may also be the case for the L cone photopigment, as the rate of spontaneous activation is much higher than that expected if the energy barrier for spontaneous activation were equal to the full energy of a 600 nm photon. These observations suggest that the energy barrier for thermal activation scales with but is less than the photon energy at the photopigment's peak sensitivity. Similarly, the energy barrier for light activation of frog rod and cone photopigments is not uniquely determined by the wavelength of the pigment's maximal sensitivity (Koskelainen et al., 2000).

The difference in the spontaneous activation rates of the rod, L cone, and S cone photopigments is an important factor controlling the amplitude and kinetics of each cell's single photon response. Figure 6 compares estimated single photon responses from a representative rod, S cone, and L cone. The single photon response of the dark-adapted S cone more closely resembles that of the rod than that of the L cone. Thus, the S cone transduction cascade, with its relatively low rate of spontaneous pigment activation, amplifies the signal initiated by photoisomerization of a single photopigment molecule to nearly the same extent as the rod transduction cascade. The L and S cone single photon responses became similar in the presence of a steady light that overwhelmed spontaneous pigment activation (Figure 4). Thus, the inability of L cones to completely dark adapt because of the spontaneous activity of their photopigment may explain much of the difference between their single photon responses and those of the S cones and rods.

The different amplitudes and kinetics of the elementary light responses of the L and S cones suggests corresponding differences in how the visual system processes the L and S cone signals. For example, signal transfer from rods to second-order cells in the dark-adapted retina is matched to the temporal characteristics of the rod signal and noise, so that each temporal frequency is weighted by its signal-to-noise ratio (Bialek and Owen, 1990). If signal transfer from cones to second-order cells implements a similar matched filtering, the kinetics of signal transfer should differ for dark-adapted L and S cone signals due to the differences in the respective signal and noise spectra. The differences in signal transfer should decrease in the presence of steady light that renders the L and S cone signal and noise spectra similar. Individual S cones will also provide reliable input signals to the retina at lower light levels than the L cones because of their lower noise and larger single photon responses. Thus, retinal cells sensitive to changes in luminance might weight S cone responses more heavily than those of L cones in darkness but attach similar significance to signals from the two cone types in the presence of background light.

Experimental Procedures

The outer segment membrane current of salamander L and S cones was recorded with suction electrodes. Recording techniques and tissue preparation followed procedures described elsewhere (Rieke and Baylor, 1996). For experiments on intact cells, the Ringer's solution contained (in mM) 80 NaCl, 2 KCl, 35 $NaHCO_3$, 1 $CaCl_2$, 1.6 $MgCl_2$, 10 glucose, and 3 HEPES (pH 7.4 when equilibrated with 5% CO_2/95% O_2). The solution filling the suction electrode was identical except that the $NaHCO_3$ was replaced with NaCl. In experiments on truncated outer segments the outer segment and most of the ellipsoid were drawn into the suction electrode. The inner segment was then severed with a sharp glass probe to provide diffusional access to the interior of the outer segment. In truncation experiments the suction electrode contained (in mM) 120 NaCl, 0.05 $CaCl_2$, 1.6 $MgCl_2$, 3 HEPES, and 1 EGTA (pH 7.4 with NaOH); the dialyzing solution contained 120 arginine-glutamate, 0.75 $CaCl_2$, 1.6 $MgCl_2$, 3 HEPES, 1 BAPTA, and 0.1 ATP (pH 7.4 with NMG-OH). GTP and cGMP were added to the dialyzing solution as indicated. Solution changes were achieved with a series of electronically controlled valves whose outlets were connected to a common perfusion pipe.

Light stimuli were delivered from a dual beam optical bench. Monochromatic lights were obtained by passing the light from a tungsten-halogen bulb through interference filters with 10 nm nominal bandwidths. Salamander L, S, and ultraviolet-sensitive cones have peak sensitivities at 600, 430, and 360 nm (Makino and Dodd, 1996) and are readily identified by the relative amplitudes of their responses to 620, 440, and 380 nm lights: L cones are 4 times more sensitive to 620 nm than 440 nm light; S cones are 105 times more sensitive to 440 nm than 620 nm light; and ultraviolet cones are 40 times more sensitive to 380 nm than 440 nm light (Makino and Dodd, 1996). After identification we used 440 nm light for stimulation of S cones and 620 nm light for stimulation of L cones. Ultraviolet-sensitive cones were not studied. Light intensities were controlled with a set of calibrated neutral density filters, and light flashes were produced by an electronically controlled shutter in the light path.

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