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Comparison of the Light-Sensitive and Cyclic GMP-Sensitive Conductances of the Rod Photoreceptor: Noise Characteristics

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Patch-clamp recordings were made from outer segments of single rod photoreceptors isolated from toad retina. Cyclic GMP (cGMP) and its hydrolysis-resistant analog, 8-bromo-cGMP, increased the conductance of excised membrane patches when applied to the intracellular face of the membrane but not when applied to the extracellular face. The rectification properties of the cGMP-dependent conductance depended on the concentration of divalent cations bathing the intra- and extracellular membrane faces. Current flow was favored from the side of the membrane, either internal or external, that was exposed to bathing fluid free of divalent cations. The power spectral density of cGMP-induced noise was fitted by a sum of 2 Lorentzian components, with corner frequencies differing approximately 15-fold on average. This suggests that channel gating is controlled by 2 kinetic components.

To compare the cGMP-sensitive conductance with the light-sensitive conductance of the rod, cell-attached patch-clamp recordings were made from intact, dark-adapted rods, and noise arising from the light-sensitive conductance was analyzed. The power spectrum of the light-sensitive noise also exhibited 2 Lorentzian components similar to those of the cGMP-sensitive conductance in excised patches. These results are consistent with the idea that cGMP opens the light-sensitive channel of the rod outer segment.

Visual transduction in rod photoreceptors requires a diffusible internal transmitter that mediates the effect of light on plasma membrane conductance. One suggested mechanism of transduction holds that guanosine 3':5'-cyclic monophosphate (cGMP) is the internal transmitter. In this view, cGMP keeps the light-sensitive conductance of the plasma membrane open in the dark; light decreases the conductance by activating a cGMP-phosphodiesterase, which reduces the internal concentration of cGMP and thus causes channels to close. In agreement with the idea that cGMP is the internal transmitter, Fesenko et al. (1985) have reported recently that cGMP opens channels in excised patches of rod membrane. This action of cGMP appears to be a direct agonist interaction with the channel, not requiring nucleoside triphosphate cofactors, and thus not mediated via protein phosphorylation. However, light-adapted rods were used in these experiments, so it was impossible to determine the similarity of the cGMP-dependent conductance to the light-sensitive conductance of the intact cell or even to establish that the excised patch of membrane had contained functional light-sensitive conductance when still attached to the rod.

To test the linkage between the light-sensitive conductance and the cGMP-sensitive conductance, I have conducted experiments comparing the noise properties of the cGMP-sensitive conductance of excised patches and the light-sensitive conductance of dark-adapted rods under similar experimental conditions. Results indicated that the kinetics of the 2 conductances are similar and that both are more complex than expected from a 2-state channel. This similarity suggests that cGMP opens the light-sensitive conductance in excised patches of photoreceptor membrane.

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Materials and Methods

Experiments were performed on isolated rod photoreceptors obtained from *Bufo marinus* retina as described previously (Hodgkin et al., 1984; Matthews, 1985c). In some experiments, the inner segment and part of the outer segment of an isolated rod were drawn into a suction electrode (Baylor et al., 1980) to record the macroscopic dark current and to support the rod mechanically, and a patch pipette (Hamill et al., 1981) was placed on the protruding outer segment. In other experiments, only the patch pipette was used. Patch pipettes were pulled from thick-walled, hard-glass tubing (Pyrex; o.d. = 1.2 mm; i.d. = 0.6 mm) and had resistances of 20–50 MΩ when filled with toad Ringer's solution. The outside diameter of pulled pipette tips was 0.5–1.0 μm. All experiments were performed at room temperature (21–27°C).

Seal formation

Under visual control, the patch pipette was advanced perpendicular to the long axis of the rod until it just touched the side of the outer segment. At that point, gentle suction was applied by mouth to the pipette interior, causing sudden formation of a high-resistance seal (1–100 GΩ; typically 10–50 GΩ). Suction was immediately released upon seal formation. Light-suppressible inward current was then recorded via the patch pipette, confirming that the recording was made from the plasma membrane of a functional outer segment. In some experiments, the saline in the recording chamber contained 200 units/ml collagenase (type CLSPA; Cooper/Worthington Biomedical). In more recent experiments, including all those from which noise-analysis results are reported, no enzyme treatment was used, with no apparent effect on the rate of successful seal formation.

Solutions

Normal toad Ringer had the following composition: NaCl, 111 mM; KCl, 2.5 mM; $MgCl_2$, 1.6 mM; $CaCl_2$, 1.0 mM; glucose, 10 mM; HEPES, 10 mM; pH 7.8, with NaOH. Zero-calcium saline (0 Ca) had a similar composition, except that no calcium was added. Calcium-selective electrode measurements showed that calcium activity in the nominally calcium-free solution was 30–50 μM. In some experiments, 0.3 mM EGTA was added to the 0 Ca Ringer to give a final calcium concentration of 1–10 nM. Ringer containing no divalent cations (0 Ca, 0 Mg Ringer) contained 118 mM NaCl, 2.5 mM KCl, 10 mM glucose, 10 mM HEPES, and 0.15 mM EDTA. cGMP and 8-bromo-cGMP were obtained from Sigma. Solution changes were made via local perfusion (Liebman et al., 1984) through one or more pipettes placed near the patch pipette. In some experiments on excised patches, a rapid-flow system described by Brett et al. (1984) was used to apply solutions.

Recording and data acquisition

Patch-clamp recordings were made with a List EPC/7 or a Dagan model 8900 patch-clamp amplifier. All data were recorded on an FM tape

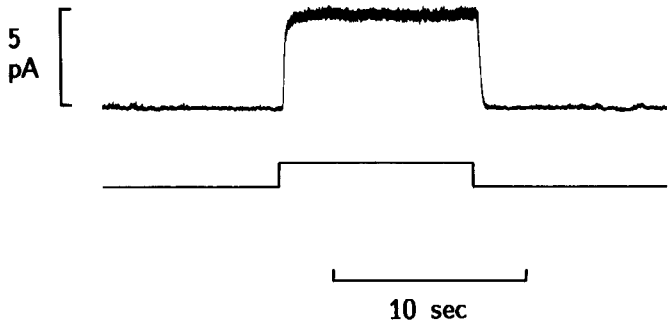

Figure 1. Effect of cGMP on conductance of inside-out patch of outer segment membrane. *Upper trace,* Patch membrane current at a steady pipette potential of −21 mV relative to bath (i.e., patch membrane potential = +21 mV). *Bottom trace,* Pulse controlling solenoid-activated 2-way pinch valve; during the upward deflection the solution flowing past the intracellular membrane face was switched from normal Ringer to normal Ringer with 0.1 mM cGMP. Patch pipette was filled with normal Ringer. Seal resistance = 50 GΩ.

recorder at 0–2500 or 0–5000 Hz bandwidth. Selected segments were later replayed through an anti-aliasing filter and digitized for computer analysis. Power spectral analysis was carried out as described by Baylor et al. (1980).

Illumination

Visible stimuli and infrared illumination for viewing manipulations were provided by a dual-channel optical stimulator described previously (Matthews, 1985d). The wavelength of visible stimuli was set to 500 nm with an interference filter. All manipulations were performed on the stage of an inverted, compound microscope equipped with an infrared-sensitive TV system.

Results

Effects of cGMP on cell-free outer segment patches

General properties of cGMP-dependent conductance

Fesenko et al. (1985) first reported that application of cGMP to the intracellular face increases the conductance of an excised patch of rod outer segment membrane, an observation that has since been repeated by others (Matthews, 1985b, e; Nakatani and Yau, 1985; Stern et al., 1985; Yau and Nakatani, 1985; Yau et al., 1985). Figure 1 shows the increase in conductance of an inside-out patch when 0.1 mM cGMP was applied to the intracellular face using a rapid-flow technique (Brett et al., 1984). The effect of cGMP was rapidly reversible and repeatable. The dibutyryl derivative of cGMP was ineffective, as shown in Figure 2*A*. This agrees with results in other systems, where dibutyryl derivatives of cyclic nucleotides are physiologically active when applied to intact cells but not when applied to cell-free systems (Henion et al., 1967). This is thought to occur because removal of butyrate from the ribose ring by intracellular esterase is required for activity of dibutyryl cyclic nucleotides. As shown in Figure 2*B*, the the 8-bromo derivative of cGMP did increase patch conductance. The resistance of 8-bromo-cGMP to hydrolysis by phosphodiesterase suggests that the effect of cGMP on cell-free patch conductance is not due to phosphodiesterase activity in the excised membrane or to products of hydrolysis.

The current–voltage relation of the light-sensitive current of intact rods exhibits pronounced outward rectification (Bader et al., 1979; Baylor and Nunn, 1983; Zimmerman and Baylor, 1985). Figure 3*A* shows that the cGMP-dependent conductance also displayed outward rectification when the extracellular membrane face was exposed to normal levels of divalent cations (1.0 mM Ca^{2+}, 1.6 mM Mg^{2+}) and the intracellular face was exposed to 0 Ca, 0 Mg Ringer. This is qualitatively similar to the free divalent cation gradient in the intact cell. However,

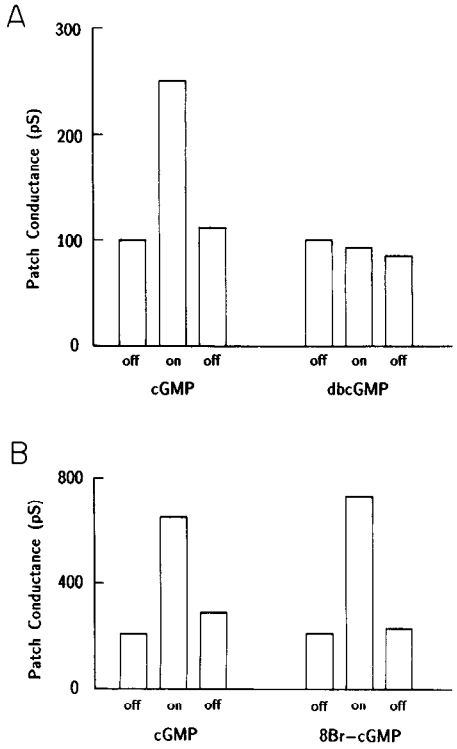

Figure 2. Comparison of effects of cGMP, dbcGMP, and 8Br-cGMP on conductance of cell-free patches of outer segment membrane. All nucleotides were dissolved in normal toad Ringer at a concentration of 1.0 mM. Perfusion was applied to the intracellular membrane face. *A,* cGMP increased patch conductance, but a subsequent application of dbcGMP did not. Patch membrane potential was −29 mV. *B,* Different patch from that in *A*. Both cGMP and 8Br-cGMP increased patch conductance. Patch membrane potential was −30 mV.

when the gradient was reversed, so that 0 Ca, 0 Mg Ringer bathed the external but not the internal face, the direction of rectification was reversed (Fig. 3*B*). Thus, more current could be passed from the solution lacking divalent cations, regardless of whether that solution bathed the intra- or the extracellular membrane face. This suggests that divalent cations are responsible for the rectification observed in the current–voltage relation of the cGMP-sensitive conductance, either by binding to and altering the channel or by entering and blocking the channel. The fact that divalent cations act from either membrane face provides some evidence in favor of the latter.

In some experiments, outside-out excised patches were formed after recording from rods in whole-cell patch-clamp configuration (Hamill et al., 1981). In 10 of these experiments, cGMP was applied to the extracellular membrane face at a concentration (1.0 or 1.25 mM) that would saturate the cGMP-dependent conductance if applied to the intracellular face. As illustrated in Figure 4, cGMP had no effect on patch conductance under these conditions. Thus, the cGMP-dependent conductance of the outer segment membrane is sensitive to cGMP only on the intracellular face of the membrane.

Noise properties of cGMP-dependent current

It is apparent in Figure 1 that the variance of the current increased during cGMP perfusion. To examine the relation between variance and amplitude of the cGMP-dependent current, the variance during brief (0.1 sec) samples of current was calculated during onset and decay of the effect of cGMP at the beginning and end of perfusion. To slow the rate of onset and decay so that there was little change in amplitude of current

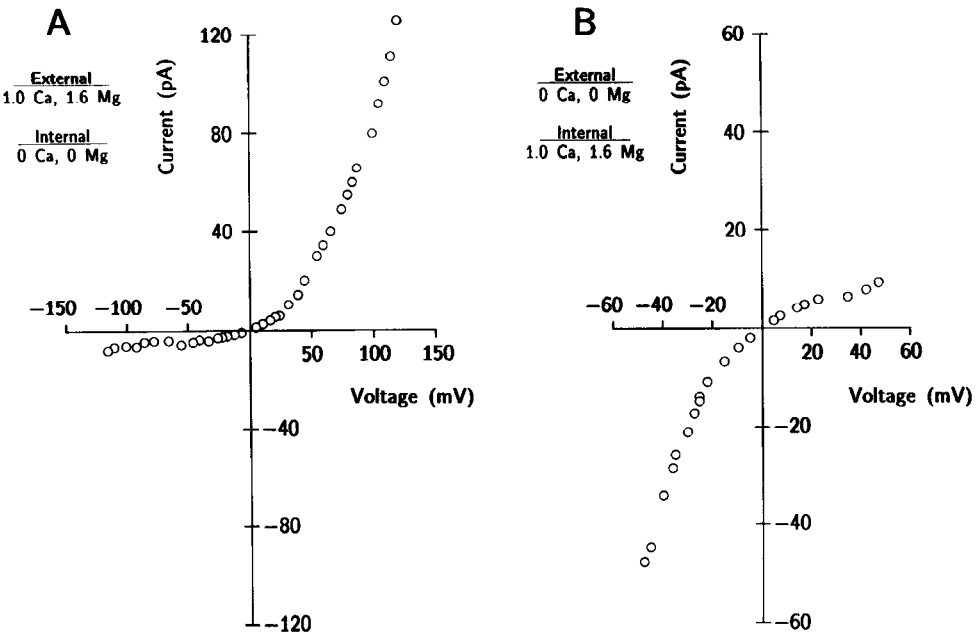

Figure 3. Effect of divalent cations on current–voltage relation of cGMP-dependent conductance of excised patches of outer segment membrane. *A*, Extracellular solution contained 1.0 mM Ca and 1.6 mM Mg, while the intracellular solution had no added calcium or magnesium and 0.15 mM EDTA. The conductance exhibited outward rectification. *B*, Different patch from that in *A*, with 0 Ca, 0 Mg solution on the extracellular face and 1.0 mM Mg on the intracellular face. The cGMP-dependent conductance showed inward rectification under these recording conditions. In both *A* and *B*, sodium and potassium ions were symmetrically distributed.

during the brief sample, the rapid flow technique of Figure 1 was not used in these experiments. Instead, cGMP was applied by placing a perfusion pipette near the patch electrode bearing an inside-out patch of outer segment membrane. The perfusate contained a saturating concentration of cGMP (either 1.0 or 1.25 mM). Perfusion was terminated by moving the perfusion pipette away from the patch pipette. Results from an experiment of this kind are shown in Figure 5. The variance increased as the amplitude of the cGMP-dependent current increased, up to saturation of the current. Such behavior would not be expected if the action of cGMP were similar to that of ACh at the neuromuscular junction, where such a linear relation between mean and variance of current is expected only when conductance is low relative to maximum conductance (Anderson and Stevens, 1973). If saturation of the cGMP-dependent current occurred when all channels were open and if the channel had only 2 states (open and closed), variance would be low at saturation and maximal at an intermediate level of current (Sigworth, 1980). Possible explanations of the deviation from this expectation will be considered in the Discussion.

The power spectrum of the cGMP-dependent noise was obtained by subtracting the spectrum in the absence of cGMP from that in the presence of cGMP. In order to increase the magnitude of the cGMP-dependent conductance, and thus the resolution of the noise measurements, all experiments discussed in this section were conducted with 0 Ca, 0 Mg Ringer on the external face of the membrane (i.e., inside the patch pipette). The power spectral density of the cGMP-dependent noise could be described by a sum of 2 Lorentzian components:

$$S(f) = S_l(0)/[1 + (f/f_l)^2] + S_h(0)/[1 + (f/f_h)^2] \quad (1)$$

where $S(f)$ is power spectral density at frequency f, $S_l(0)$ and $S_h(0)$ are the zero-frequency asymptotes of the low- and high-frequency components, and f_l and f_h are the half-power, or corner, frequencies of the 2 components. As shown in Figure 6,

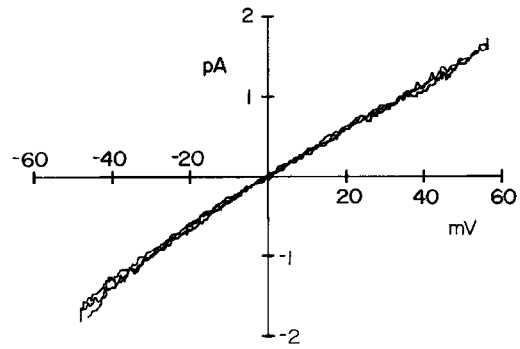

Figure 4. Voltage–current relations from outside-out, cell-free patch obtained following whole-cell recording from an isolated rod. The indistinguishable curves show relations before, during, and after perfusion of the extracellular face of the patch with normal Ringer + 1.0 mM cGMP.

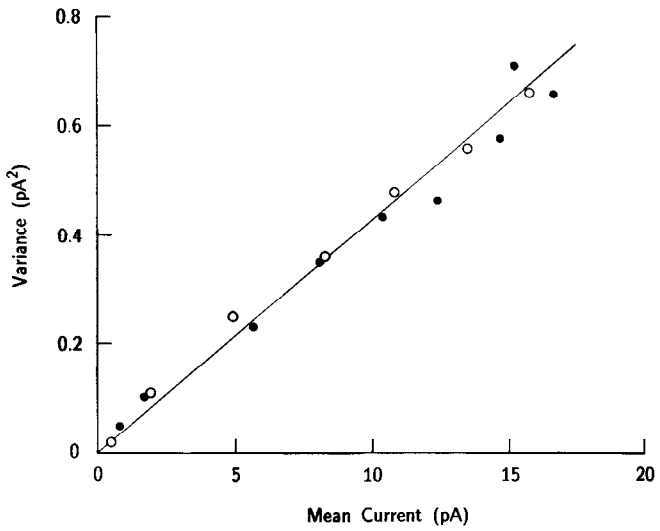

Figure 5. Relation between variance and mean of cGMP-dependent current during the decay of current following the termination of perfusion of the intracellular face with 1.0 mM cGMP (*open circles*) or 1.25 mM cGMP (*filled circles*). Baseline variance was subtracted. Patch membrane potential = −32.5 mV.

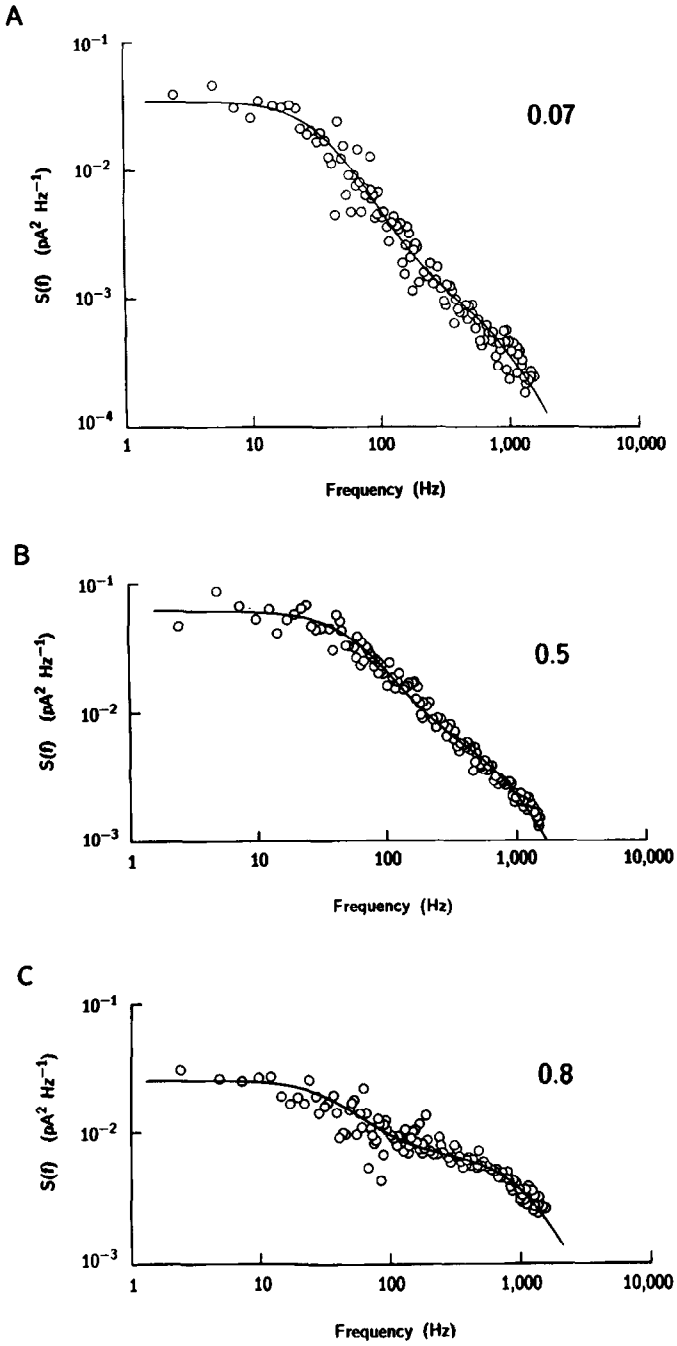

Figure 6. Power spectral density of cGMP-dependent membrane current noise at 3 levels of current. Numbers on the face of each graph give mean current divided by maximal current. Spectrum of background noise subtracted in each case. Power spectra were calculated from 0.4096 sec samples of membrane current, digitized at 0.2 msec intervals after low-pass filtering at 2000 Hz (6-pole Butterworth). Number of samples was 11 (*A*), 25 (*B*), or 18 (*C*). Data points are averages of individual frequency points as follows: <100 Hz, individual points; 100–200 Hz, 2 points; 200–500 Hz, 5 points; >500 Hz, 10 points. *Solid lines* in each panel were drawn according to equation (1) with the following parameters. *A*: $S_l(0) = 3.4 \times 10^{-2}$ pA² Hz⁻¹, $f_l = 36$ Hz, $S_h(0) = 8.4 \times 10^{-4}$ pA² Hz⁻¹, $f_h = 720$ Hz. *B*: $S_l(0) = 5.5 \times 10^{-2}$ pA² Hz⁻¹, $f_l = 56$ Hz, $S_h(0) = 5.5 \times 10^{-3}$ pA² Hz⁻¹, $f_h = 728$ Hz. *C*: $S_l(0) = 1.88 \times 10^{-2}$ pA² Hz⁻¹, $f_l = 40$ Hz, $S_h(0) = 6.75 \times 10^{-3}$ pA² Hz⁻¹, $f_h = 1000$ Hz.

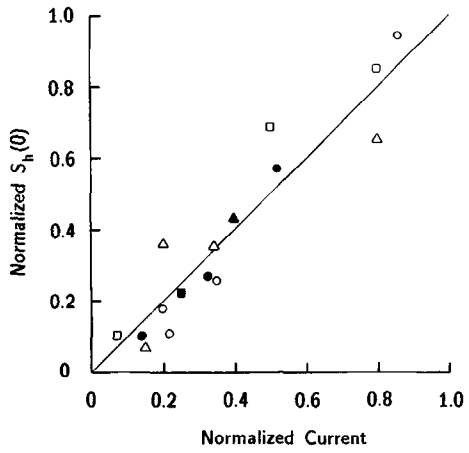

Figure 7. Relation between mean cGMP-dependent current and zero-frequency asymptote of high-frequency component of noise power spectral density [$S_h(0)$]. Each symbol type shows results from a different experiment. To compare results across experiments, $S_h(0)$ and mean current were normalized in each case by dividing by their maximal values at a saturating level of cGMP.

the relative contributions of the 2 components varied with the level of saturation of the cGMP-dependent current. At low levels of conductance (Fig. 6*A*), the high-frequency component was relatively minor, but as saturation was approached, it became more pronounced (Fig. 6, *B, C*). This increase in the high-frequency component underlies the steady rise in variance observed as cGMP-dependent current increased to saturation (see Fig. 5). A convenient index of the contribution of the high-frequency noise component is the zero-frequency asymptote, $S_h(0)$, obtained from fitting equation (1) to the power spectrum. $S_h(0)$ increased from 8.4×10^{-4} pA² Hz⁻¹ (Fig. 6*A*) to 6.75×10^{-3} pA² Hz⁻¹ (Fig. 6*C*) as the mean level of cGMP-dependent current increased from 0.07 to 0.8 of maximum. The relation between $S_h(0)$ and mean current in 6 experiments like that in Figure 6 is shown in Figure 7.

In 27 experiments, the corner frequencies for the low- and high-frequency Lorentzian components of cGMP-dependent noise averaged 70 ± 5 and 1190 ± 76 Hz (mean ± SE). These corner frequencies correspond to exponential time constants of 2.3 and 0.13 msec. The presence of 2 Lorentzian components in the power spectrum suggests 2 kinetic components in channel gating. Without single-channel recordings, however, it is not possible to specify which of a number of possible sources gives rise to the 2 components. This will be explored in more detail in the Discussion.

Light-sensitive current in cell-attached recordings from intact rods

General characteristics of light-sensitive membrane current noise

Recently, a component of dark noise that may arise in the light-sensitive channels of the outer segment membrane has been observed both in cell-attached and in whole-cell patch recordings from isolated rods (Bodoia and Detwiler, 1984, 1985; Gray and Attwell, 1985; Matthews, 1985a, b, e; Zimmerman and Baylor, 1985). To compare this light-sensitive noise with noise in the cGMP-dependent current, cell-attached patch-clamp recordings were made from intact, dark-adapted rods. Examples of membrane current recorded in this way are shown in Figures 8 and 10*A*. Light eliminated an inward current through the recorded patch and reduced the variance of the patch current. Because intracellular voltage was not controlled in these experiments, light-induced suppression of noise in patch recordings

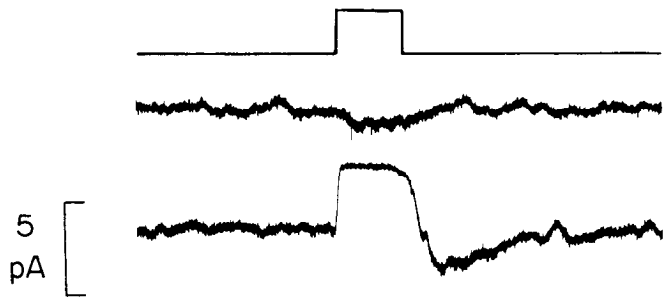

Figure 8. Effect of local illumination on noise in membrane current of cell-attached patch of intact dark-adapted rod. Light (intensity 55 photons μm^{-2} sec^{-1}) was restricted to a transversely oriented slit 5 μm wide. *Top trace,* timing of 7 sec illumination. Duration of light pulse gives time calibration. *Middle trace,* The slit was centered 30 μm from the recorded patch of outer segment membrane. *Bottom trace,* The slit was centered on the recorded patch.

might be due to closure of the light-sensitive conductance of the recorded patch or to the hyperpolarization associated with illumination. To examine this question, illumination was restricted to a narrow, transversely oriented slit, which was centered on the recorded patch of membrane or displaced 30 μm along the outer segment. Results of one such experiment are shown in Figure 8. When the slit was centered on the patch, light abolished the dark current and the dark noise; when the slit was displaced longitudinally, however, light did not affect the dark noise. The change in macroscopic dark current, and thus the resulting hyperpolarization, produced by such slit stimuli is largely independent of slit position along the outer segment (Matthews, 1985d). Therefore, the result in Figure 8 suggests that the effect of light on the dark noise depends on the reduction in patch conductance by light, rather than the associated hyperpolarization.

If the dark noise in the recorded patch indeed arises locally in the light-sensitive conductance of the patch, as suggested by Figure 8, then varying the voltage across the recorded patch of outer segment membrane should have parallel effects on the dark current and the single-channel current underlying the dark current. Specifically, a voltage change that produces an x-fold change in the dark current should change the variance of the dark current by x^2, assuming that the only effect of varying voltage is to alter the driving force for the single-channel current. Results of experiments of this type are summarized in Figure 9, which shows the change in light-sensitive variance plotted against the change in saturating light response when the holding potential inside the patch pipette was varied. On double-logarithmic coordinates, the data points clustered around the straight line expected for a square-law relation between variance and mean of the dark current. A simple interpretation is that the patch dark noise arose in the light-sensitive conductance of the recorded membrane.

Comparison of cGMP-sensitive and light-sensitive noise

To compare the light-sensitive noise in cell-attached patch recordings with the cGMP-sensitive noise of excised patches, the power spectrum of the light-sensitive noise was obtained by subtracting the spectrum in bright light from the spectrum in darkness. So that recording conditions would be comparable to those in the studies of excised patches discussed above, patch electrodes in these experiments were filled with 0 Ca, 0 Mg Ringer. An example of the power spectrum of light-sensitive noise is shown in Figure 10*B*. Like the cGMP-dependent noise, the spectrum of the light-sensitive noise could be fitted by a sum of 2 Lorentzians [equation (1)]. In 22 experiments of this kind, the low- and high-frequency corner frequencies averaged 90 ± 5 and 1000 ± 100 Hz (mean ± SE). These are similar to

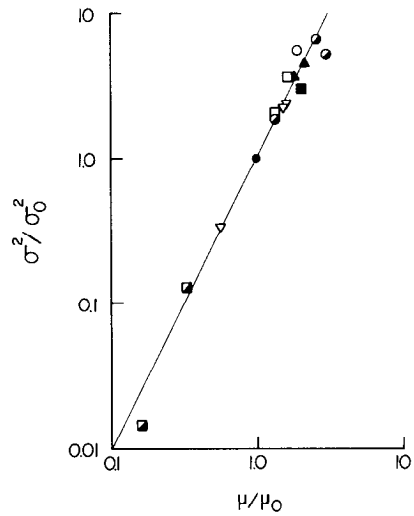

Figure 9. Double-logarithmic plot of the relation between variance of dark noise and amplitude of the dark current as both were varied by changing the patch polarization. Cell-attached recording from outer segment of dark-adapted rods. Dark current was taken to be equal in magnitude to the saturating light response. To compare the results across experiments, both the amplitude (μ) and variance (σ^2) of the dark current were normalized for each experiment relative to their values with no pipette holding potential (μ_0 and σ_0^2). Thus, the *filled circle* represents the normalized resting state, a point shared by all experiments. Each of the other symbol types shows results from a different experiment. The *straight line* shows the expected relation if the change in variance were proportional to the square of the change in dark current.

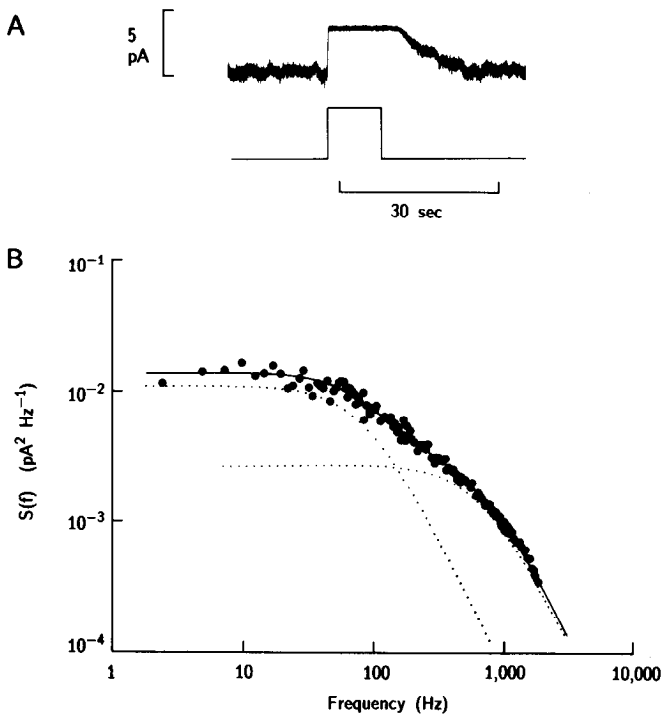

Figure 10. Power spectral density of dark noise in patch membrane current. *A,* Chart-recorder trace showing effect of light on membrane current. Timing of illumination (320 photons μm^{-2} sec^{-1}; wavelength = 500 nm) shown by *lower trace.* Bandwidth, 0–80 Hz. Patch hyperpolarized by 21 mV. *B,* Difference spectrum of light-suppressible noise. *Solid line* through data points was drawn according to equation (1) with $S_l(0) = 1.08 \times 10^{-2}$ pA^2 Hz^{-1}, $f_l = 80$ Hz, $S_h(0) = 2.7 \times 10^{-3}$ pA^2 Hz^{-1}, and $f_h = 640$ Hz. *Dotted lines* show the 2 single-Lorentzian components.

the values of 70 Hz for f_l and 1190 Hz for f_h obtained from power spectra of cGMP-dependent noise of excised patches. This suggests that the cGMP-sensitive and light-sensitive channels are kinetically similar. The ratio of zero-frequency asymptotes of the high- and low-frequency components, $S_h(0)/S_l(0)$, of the light-sensitive noise averaged 0.17 ± 0.02 (mean ± SE) in the 22 experiments. This is comparable to the relative zero-frequency asymptotes of the 2 components of cGMP-dependent noise at low levels of conductance (see Fig. 6*A*), suggesting that the light-sensitive conductance is small relative to the maximum value that would be reached if all channels were open.

Discussion

The noise properties of cGMP-dependent and light-sensitive conductances of the rod photoreceptor revealed similarity in the kinetics of the underlying channel. In both cases, the noise power spectrum was fitted by a sum of 2 Lorentzian components, with similar high- and low-frequency corner frequencies for the 2 conductances. These results are consistent with the idea that the channel opened by cGMP in the excised patch is the same as the channel closed by light in the intact rod.

The fact that 2 Lorentzian components were observed in noise power spectra suggests 2 components of channel gating but does not specify which of a number of possible physical models might apply. For example, 2 Lorentzian components might arise because of 2 populations of channel open time or closed time, one brief and one longer, or from a rapid component of gating revealed during agonist-induced channel opening (flicker). The latter occurs, for example, during channel block in other systems (Colquhoun and Sheridan, 1981; Ogden and Colquhoun, 1985; Ogden et al., 1981; Yellen, 1984), so that the current rapidly flickers when the channel is open, producing a high-frequency component of noise. In this regard, another observation of interest is the finding that variance of cGMP-dependent current increased steadily up to saturation of the conductance. This would not be expected under a scheme in which the probability of a channel being open approaches 1.0 at a saturating level of cGMP. In such a scheme, variance would be expected to be low both at low levels of macroscopic current, when channel openings are few, and at saturation, when channel closings are few (Sigworth, 1980). Variance would be maximum at an intermediate level of current. Instead, the observed relation between mean and variance of the cGMP-dependent current suggests that the probability of channel opening was considerably less than 1.0 at maximum. Such a situation might arise, for example, if the channel flickers while in the agonist-induced open state. Each channel that binds cGMP and opens would then contribute a component of variance to the macroscopic current, because of the flicker. As the concentration of cGMP rises, the number of channels contributing variance increases, so the mean and variance rise steadily until saturation is reached. This scheme is also consistent with the observed increase in the zero-frequency asymptote of the high-frequency component of the cGMP-dependent noise as the mean level of current increased (Figs. 6, 7). This is as expected if the high-frequency component represents channel flicker and the number of contributing channels rises as saturation is approached. These observations suggest, but do not conclusively demonstrate, that the cGMP-dependent channel flickers in the open state. By extension, the light-sensitive channel is likely to behave similarly. Conclusive evidence on this issue will require resolution of channel activity at the single-channel level.

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